A Critical Review of the Research and Treatment of Hepatitis C Virus (HCV) and Hepatitis & HIV Coinfection

The Hepatitis Report
July 9-14, 2000

by Michael Marco and
Jeffrey Schouten, M.D.
From Treatment Action Group

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Credits & Acknowledgments

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The Treatment Action Group (TAG) fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care, and information they need to save their lives. TAG focuses on the AIDS research effort, both public and private, the drug development process, and our nation's health care delivery systems. We meet with researchers, industry, and government officials, and resort when necessary to acts of civil disobedience, or to acts of Congress. We strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

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This report is dedicated to the memory of
Michael Wright
(1953 - 1992)
&

Bill Thorne
(1963 - 1999)

"The disease generally progresses at a snail's pace, requiring the passage of 3 to 4 decades, in most instances, to reach recognizable serious endpoints. It therefore represents a daunting task for the clinical investigator, few of whom are willing to devote their research careers to this exhaustive form of investigation."
-- LB Seeff, Hepatology 1997; 26:21S-28S.

"Because of the ageing phenomena, all [natural history] studies which do not take into account both the age at infection and the duration of infection are meaningless."
-- T Poynard, e-mail correspondence, 23 June 2000.

"The patient who has a liver disease wants (or needs) to know about the natural history of the disorder so as to plan for the future. The patient should be informed regarding the likely consequences, important milestones, major complications, and available therapies, all given with a large measure of compassion and sensitivity."
-- WC Maddrey, AASLD, Postgraduate Course, 1999.

"Physicians and patients must carefully weigh the risks (which are clinically significant in the case of treatment with interferon alfa-2b and ribavirin), the benefits (moderate in this instance), and the cost (substantial in this instance) of any treatment option for a disease that has emerged as an important public health problem."
-- TJ Liang, N Engl J Med 1999; 340:1207.

Foreword

By Marion Peters, M.D.

July 9-14, 2000

This TAG report on hepatitis C virus (HCV) is comprehensive and will bring you completely up to date. It runs the gamut of HCV infection with areas of interest for the clinician, allied health care worker and educated patient. It contains information about epidemiology, natural history, diagnosis, pathogenesis and treatment. It is certainly an enormous task to undertake but the authors have been largely very successful. Many of the chapters contain the earliest literature in the area and are current to last month's abstracts. It may be difficult for some of us to read an abstract with the same conviction of fact, as abstracts have not been peer reviewed rigorously, nor is all the data usually available at the time presentation. However, in a fast moving field such as HCV, it allows the reader to know what is "hot" and where the field is heading. We are clearly told what data and trials are peer reviewed, which are confirmed by other investigators and which appear to be "outside the envelope" but interesting none the less. This report is generally superbly referenced and will be of great value to you.

The natural history chapter reminds us that not all patients inexorably deteriorate to end-stage liver disease, liver transplantation or death. It is clear that for the large number of years that we have been following patients, some clinicians see the slowest rates of progression whilst others see HCV as "the evil empire". Patients need to know the facts, not colored by drug company hype, or physician preference and this report provides these facts. Only by knowing that not all patients progress, can individuals patients decide whether treatment for them is now or in the future. The epidemiology, risk factors and modes of transmission are well outlined with perhaps an overabundance of information. You can skim it or dive in for the total immersion, whichever is your preference. This is an excellent chapter with clear tables, explaining the high rate of transmission in IVDU patients and the low sexual transmission rate.

The diagnosis of HCV is often complex with multiple tests and the confusion of liver biopsy evaluation. Once again the authors have used excellent available reviews and references to present readable current state-of-the-art information. The reader must be cautioned that this area is not well regulated and HCV RNA tests are changing rapidly. In addition, when tests are performed in the hospital setting or the community, often a different laboratory is used at different times (the pressures of managed care). In these cases, one cannot extrapolate from one bDNA to another PCR or even from one PCR to another. Therefore, it is critical that patients and clinicians not put excessive weight on small (less than one log) changes. HCV RNA will change little from patient to patient but a lot from test to test.

The area of co-infection with HIV is the youngest in the field and is a moving target. Large cohort studies are lacking and treatment trials are small in number and patient size. This is an area that is receiving a large amount of attention; treatment trials are underway and more hepatologists are becoming involved working side-by-side with infectious disease specialists. The role of HCV in response to HIV therapy is largely unknown. Viral dynamics

of HCV is in its infancy, compared to that of HIV. Markers of response to HCV have included genotype, age of acquisition, gender, viral load and amount of fibrosis on liver biopsy. Early studies suggest that these may be superceded by viral dynamics: those with rapid response to interferon therapy are more likely to achieve a sustained response versus those who are slow responders. Only time will tell if this sweeping statement is correct.

The chapters on experimental therapies and current treatment are excellent. Once again we are reminded that at best only half of HCV patients respond to current therapies. But only half may need therapy in the long term. Unfortunately clinicians cannot determine which patients will progress to fibrosis and end-stage liver disease and so most patients are treated especially if they have some scarring without cirrhosis. This is an area that requires intensive research from clinical, epidemiological and immunological aspects. Interferon remains the mainstay of therapy with pegylated IFNs providing exciting new advances. By combining IFN to polyethylene glycol, IFN remains in the circulation longer and thus only weekly dosing is required. This results in ease of treatment as well as an apparent higher response rate, including a surprisingly high rate in cirrhotics (<10% in all studies before pegylated IFN). We may need to look carefully at these studies when they are published but early reports are very encouraging. Side effects are not much different from those of daily dose interferon although there may be some populations in whom dose finding is necessary before putting patients on long- acting weekly IFN. Newer therapies aimed at the virus itself have been slow in coming but are clearly the next line of drugs. In particular, ribozymes may be the next "breakthrough" in this area. Immunomodulators have been generally less promising with the exception of IL-10 as an anti-fibrotic.

I would recommend this report highly to those who want to be fully informed about the area. Those who need full references; those who may not have the time or inclination to gather the oldest and the latest information; and those who need to delve more deeply into particular areas of this fascinating field will find this report useful. Many scientists and clinicians have worked with Michael Marco to address specific areas of their expertise. It is a testament to them and to Michael that he has produced this informative but easily readable document. Not all of the statements in this report have been validated. You will not agree with all of them. But you will be stimulated to learn more and to keep abreast of new developments after reading these all encompassing chapters. You may not concur with all of the TAG policy recommendations but you will be forced to re-evaluate and think about many important issues surrounding HCV. Good luck and enjoy.

Marion Peters is Professor of Medicine and Chief of Hepatology Research, at the University of California, San Francisco.

Introduction

By Michael Marco

> "Clearly the problem of HCV will require a responsible partnership of public and private organizations. . . . If we are to make progress against this perplexing epidemic, careful and disinterested voices must prevail."1
>
> "Despite the wide publicity about hepatitis C in the media, and the numerous educational conferences and publications in the medical literature, and the dissemination of the NIH consensus statement on hepatitis C, there are significant deficits in the knowledge of primary care physicians regarding hepatitis C."2

My appreciation of and desire to study hepatitis C virus (HCV) research is something new. It started off as mere curiosity during my research of AIDS-related opportunistic infections (OIs) when I thought about adding a short chapter on HCV to TAG's OI Report because it was well known that many individuals with HIV are also coinfected with HCV. Approximately two years later, it seems laughable that one could simply write a "short chapter" on HCV. It has become apparent to me that there is a need for a thorough study, review and critical analysis of HCV research.

Many AIDS treatment advocates have critically analyzed the numerous facets of HIV clinical and basic research with great aplomb. They have produced a wealth of patient-readable HIV treatment information so that people with HIV/AIDS can become experts in understanding their virus. In my two years of researching HCV, I found that there were only a few HCV treatment advocates, yet none had created one text that contained a complete overview of the virus, analyzed the research, and offered important and sound HCV treatment information as well as policy recommendations to move the field of HCV research forward. Since I have been well trained and mentored in researching and writing such documents on HIV-related complications, I felt I would initiate TAG's Hepatitis Project and write a report on HCV, as well as on hepatitis and HIV coinfection. People with HCV deserve the same tools as those with HIV so that they can become experts about their virus.

I quickly realized that people with HCV were not the only ones who needed to become experts. I found that many primary care physicians lack a complete breadth of knowledge of the epidemiology and clinical management of HCV. This was blatantly obvious in the 1999 Hepatology article, "Current Practice Patterns of Primary Care Physicians in the Management of Patients with Hepatitis C" by Shehab and colleagues from Anna Lok's group at the University of Michigan2. In a survey of over 400 primary care physicians from the Detroit area, 20% and 8%, respectively, considered blood transfusion in 1994 and casual household contact as significant risk factors for HCV; 43% overestimated the likelihood of a sustained response to a course of interferon therapy, while 29% had no idea what the sustained response rate was; 38% would not a refer an HCV antibody-positive patient to a gastroenterologist even though they had no experience in treating HCV patients on their own. Another study by Villano and colleagues from Johns Hopkins found that a majority of the intravenous-drug-using patients in their natural history cohort tested HCV antibody-

positive their first time on study yet were under the care of clinic or primary care physicians3. This striking lack of awareness by health care providers about HCV epidemiology, risk factors and clinical management is unacceptable. Let us hope that this report gets into the hands of the physicians and patients who need it.

I also wrote the report in an attempt to quell the mass hysteria about HCV created by major weekly news magazines as well as by the obnoxious "get tested, get treated" HCV advertising campaign of a greedy pharmaceutical company. The push to immediately treat everyone who tests positive for HCV made my blood boil, because that is often the same message given to those who initially test positive for HIV. For HIV, we have only clinical endpoint studies documenting a survival advantage to starting potent, combination antiretroviral therapy before a patient's CD4 count drops below 200 cell/m3, yet with both viruses, we still have not fully answered the question, When should one initiate antiviral therapy? (i.e., "When to start?").

This HCV report attempts to answer that question and documents what we know and what we don't know about the epidemiology, natural history, diagnosis, and treatment of HCV. After an exhaustive analysis of peer-reviewed articles, over 40 researchers, clinicians, primary care physicians, government heath administrators, industry representatives, and patients with viral hepatitis were interviewed. Research and treatment policy recommendations have been issued and will need to be implemented in order to carefully find answers to the many basic and clinical science questions in HCV research.

This large report -- which will grow still larger in version 2.0 to include an analysis of the research and treatment of hepatitis viruses A and B (HAV and HBV) -- is a collaborative effort. Jeffrey Schouten was a great partner who worked with me over these two years, and he wrote selected HCV chapters and the section on hepatitis and HIV coinfection. Expert hepatitis researchers, including Marion Peters, Thierry Poynard, Teresa Wright, Jay Hoofnagle, Leonard Seeff, and Douglas Dieterich went out of their way in varying capacities to help me, an AIDS treatment advocate they had never met.

More collaborative and concentrated efforts on the part of industry, physicians, government, and the hepatitis community alike are needed if we are to effectively challenge, overcome, and cure HCV.

The Lancet. Making sense of hepatitis [editorial]. Lancet 352:1485, 1998.

Shehab T, Sonnad SS, Jeffries M, et al. Current practice patters of primary care physicians in the management of patients with hepatitis C. Hepatology 30:794-800, 1999.

Villano SA, Vlahov D, Nelson KE, et al. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology 29:908-14, 1999.

Epidemiology, Modes of Transmission, and Risk Factors for Hepatitis C Virus (HCV)

By Michael Marco

> "My opinion is that we just can't tell for sure about some of this because we are bad at measuring human behavior." -- Davis Thomas, e-mail correspondence

Background

During the 1970s and 1980s, no one knew what was causing hepatitis in certain individuals who had received blood transfusions. Screening tests for hepatitis A (HAV) and hepatitis B (HBV) in the mid-1970s revealed that about 25% of these cases of transfusion-associated hepatitis (TAH) were linked to hepatitis B but not hepatitis A. The remaining 75% of TAH cases, by default, were termed non-A-non-B hepatitis (NANBH) (H. Alter 1999). Ten to twenty percent of individuals who had received multiple blood transfusions (or used plasma products) developed NANBH, with a relative risk of 0.45% per unit transfused (Donahue 1992).

Because primary infection was usually asymptomatic or, at worst, mild, clinicians did not initially consider NANBH to be a very serious disease. It was soon recognized, however, that the seemingly benign NANBH could develop into a chronic hepatitis with markedly elevated liver enzymes. Sometimes the hepatitis resulted in cirrhosis.

According to the National Institutes of Health's (NIH) Harvey Alter, attitudes to NANBH changed in the late 1980s:

> The NANBH agent remained a virologic enigma . . . until researchers at the Chiron Corporation used an ambitious molecular approach on large volumes of high-titer infectious chimpanzee plasma from the Centers for Disease Control and Prevention (CDC). They extracted RNA, cloned it into an expression vector, and screened the expressed product with presumed immune sera. A single positive clone was found in the millions screened, and, within a year, the entire genome was sequenced and the agent was identified as a novel flavivirus the hepatitis C virus (HCV). (HJ Alter 1999).

In 1988 Choo and colleagues characterized the hepatitis C virus (HCV), and shortly thereafter, an antibody test was developed to detect infection (Choo 1989; Kuo 1989). When NIH researchers performed HCV assays on archived blood samples, it was determined that 70% to 90% of NANBH cases were actually HCV infections.

Prevalence of HCV Infection in the United States (U.S.)

HCV is considered the most common blood-borne infection and is one of the leading causes for liver transplantation among adults in the U.S. After the HCV antibody test became available, epidemiology studies were performed to ascertain the incidence of the infection. The original studies, however, were considered flawed because they were conducted with

first-time blood donors, individuals who had already been screened for risk factors such as infectious diseases.

A recently published study by Miriam Alter and colleagues from the Centers for Disease Control and Prevention (CDC) reported that an estimated four million persons nationwide are HCV-antibody-positive (ab+), indicating exposure to the virus. Roughly three-quarters of these have detectable HCV RNA, indicating chronic infection (MJ Alter 1999b). These data hail from the CDC's third National Health and Nutrition Examination Study (NHANES III), conducted between 1988 and 1994, and involving a sample of almost 40,000 persons between the ages of 2 and 89 years.

Out of this group, 21,241 individuals agreed to be both interviewed and tested for antibodies to HCV; of these, 1.8% were found to be HCV-antibody-positive. For the entire U.S., this corresponds to approximately 3.9 million residents infected with HCV. Below is a breakdown of the prevalence of HCV-antibody-positivity classified by race or ethnic group and gender.

Prevalence of Antibody to HCV (Anti-HCV) According to Race or Ethnic Group & Gender in NHANES III

Characteristic	No. Tested	Prevalence (%) of Anti-HCV+ (95% CI)	Estimated No. Infected Nationwide (95% CI)
All Subjects	21,241	1.8 (1.5-2.3)	3,875,000 (3,102,000-4,840,000)
Race/Ethnic Group			
Non-Hispanic White	7,965	1.5 (1.1-2.0)	2,359,000 (1,774,000-3,137,000)
Non-Hispanic Black	6,119	3.2 (2.6-4.0)*	762,000 (609,000-953,000)
Mexican Americans	6,268	2.1 (1.7-2.6)	261,000 (210,000-323,000)
Other	889	2.9 (1.4-5.8)	493,000 (245,000-993,000)
Gender			
Male	10,076	2.5 (2.0-3.2)**	2,586,000 (2,012,000-

			3,323,000)
Female	11,165	1.2 (0.9-1.6)	1,289,000 (967,000-1,717,000)

* P<0.05 for comparison with non-Hispanic whites (MJ Alter 1999b)
** P<0.05

HCV Prevalence in Blood Donors in Southern Europe

Several large HCV epidemiology studies have been published in Italy, France, and Spain. Below is a breakdown of anti-HCV prevalence in selected studies that have been conducted since the early 1990s.

HCV Incidence Rates in Six Large Southern European Cohorts

N =	Anti-HCV +	Country (Study)
173,038	0.63%	France (Anuelles 1992)
60,960	0.69%	France (Aymard 1993)
30,231	1.2%	Spain (Esteban 1991)
46,741	1.12%	Spain (Salmeron 1996)
55,587	0.93%	Spain (Munoz-Gomez 1996)
6,917	3.2%	Italy (Bellentani 1994)

HCV Prevalence in Egypt

With an estimated HCV infection rate of 25%, Egypt has a higher incidence of HCV infection than any other country in the world (Arthur 1997). The Nile Valley area has higher rates of infection compared to cities and desert areas. The Egyptian HCV epidemic is a result of a widespread treatment campaign against schistosomiasis, an ancient parasitic disease. From the 1920s to the 1980s, the government administered parenteral antischistosomal therapy (usually 6-12 injections) with reusable syringes (Frank 2000). With course of injections taking two to four weeks, an individual infected early in treatment could then spread HCV on a subsequent injection to others who used the same syringe.

Modes of Transmission and Risk Groups

Numerous epidemiology studies have documented that individuals from high-risk groups, including recipients of blood transfusions before 1991, hemophiliacs, intravenous drug users (IDUs), homosexuals, and alcohol abusers have an exceedingly high prevalence of HCV antibodies.

Blood Transfusion Recipients and Hemophiliacs before 1992

In the mid-1960s, the rate of post-transfusion hepatitis was greater than 20% (HJ Alter 1972). When donor blood in the U.S. began to be screened and excluded for antibodies to HAV, HBV, and HIV between 1985-1990, the rate of new HCV infections declined by more than 50%, lowering the risk of HCV seroconversion to 1.54% per transfusion patient or to 0.19% per unit transfused (Donahue 1992). In May 1990, a first-generation enzyme immunoassay EIA-1 was introduced to screen U.S. blood donors. It was soon replaced by the much more sensitive multiantigen test (EIA-2) in July 1992. The EIA-2 has dramatically reduced the risk of HCV infection, lowering rates to 0.001% per unit transfused (Schreiber 1996). According to Harvey Alter:

The impact of HCV blood donor screening has been enormous. The single-antigen first-generation enzyme immunoassay (EIA-1) prevented 40,000 HCV infections within the first year, and the second-generation assay (EIA-2) has actually reduced new transfusion-related HCV infections to almost zero. (HJ Alter 1999)

Before 1985, the rate of HCV infection in hemophiliacs who received clotting factor concentrates prepared from plasma pools was at least 90% (CDC 1998). Factor VIII and Factor IX, which inactivated blood-borne viruses such as HCV, were introduced in 1985 and 1987, respectively.

Injection Drug Users

The rate of HCV infection among IDUs who share contaminated needles, syringes, or drug preparation equipment continues to remain high. In numerous studies conducted around the world, the incidence of HCV among IDUs ranges from 70% to 92% (Esteban 1989; van den Hoek 1990; Donahue 1991; Zeldis 1992; Garfein 1996; Broers 1998; Hershow 1998; van Beek 1998).

% Anti-HCV+	City	Source
70%	Barcelona	Esteban 1989
74%	Amsterdam	van den Hoek 1990

85%	Baltimore	Donahue 1991
72%	San Francisco/Davis	Zeldis 1992
76.9%	Baltimore	Garfein 1996
91.6%	Geneva	Broers 1998
90% (women only)	Chicago	Hershow 1998
75.6% (age <20 years)	Sydney	van Beek 1998

The risk of contracting HCV from shared injection equipment is extraordinarily high . . . and not only for long-term IV drug users. A study by Garfein and colleagues at Johns Hopkins documented that the risk of acquiring HCV infection was as high 65% for new injectors within 6 to 12 months after beginning injection drug use (Garfein 1996). The risk of acquiring HCV is markedly higher than that of acquiring other viral infections such as HIV. The same study documented a rate of HIV infection among IDUs during this brief window of only 14%.

With regard to non-injectable drug use, intranasal cocaine use was reportedly associated with HCV infection in a study conducted by Conry-Cantilena from Harvey Alter's group at the NIH (Conry-Cantilena 1996). Finding a highly significant correlation in a multivariate analysis, the author theorized that if the device shared for snorting cocaine (a straw) was contaminated with blood, it could convey virus to denuded nasal mucosa, allowing HCV to enter the bloodstream. This possible mode of transmission-referred to by some as the "bloody straw" theory -- was highly debated, and in 1998, the CDC listed intranasal cocaine users in the category of "Persons for whom routine hepatitis C (HCV) testing is of uncertain need" (CDC 1998).

It appears that this finding by Corny-Cantilena and colleagues may have been a fluke, or merely that intranasal cocaine use is a surrogate for other behavior which could foster HCV transmission. More recently Murphy and colleagues, of the NHLBI Retrovirus Epidemiology Donor Study (REDS), published a study reporting that, in a multivariate logistic regression model, intranasal cocaine use (or use of any other powered drug) was not a risk factor for HCV (Murphy 2000).

Occupational (Needlestick) Exposure

The prevalence of HCV infection in health care workers, including orthopedic, general, and oral surgeons averages 1-2% (Thomas 1993, 1996). The serocoversion rate after an unintentional needlestick injury from an HCV-positive source is ~1.8% (MJ Alter 1994;

Puro 1995). It appears that the seroconversion rate with solid needles is lower compared to needlesticks with hollow cannula devices (Puro 1995).

Percutaneous Exposure in Other Settings

While apparently rare, HCV transmission has been associated with commercial barbering, tattooing, ear piercing, and religious scarification (Tumminelli 1995; Abildgaard 1991; Thompson 1996; Conry-Cantilena 1996; Murphy 2000). Tumminelli and colleagues found that 38% of Sicilian barbers studied had antibodies to hepatitis C and suggested that shaving was a potential route of transmission. In the REDS study, Murphy and colleagues determined that religious scarification, sharing toothbrush and/or razor, having been tattooed, and having been pierced (body or ear) were all risk factors for HCV seropositivity after controlling for IVDU (OR = 3.8; 1.6; 3.9; and 2.7, respectively).

Perinatal Transmission

Most U.S. and international studies have reported the incidence of anti-HCV positivity in pregnant women to be between 0.7% and 4.4% (Marcellin 1993; Marranconi 1994; Leikin 1994; Hillemanns 1998; Resti 1998; Conte 2000). One recent perinatal transmission study from the metropolitan New York City area documented an ominous 41% anti-HCV incidence rate in a cohort of pregnant women -- 79% of whom were past or present IDUs (Granovsky 1998). The rate of HCV RNA detectability in several international cohorts of anti-HCV-positive women ranges from 65% to 72% (Resti 1998; Granovsky 1998; Conte 2000).

Reported rates of mother-to-infant HCV transmission have ranged from 0% to 36% in numerous studies, with higher rates occurring when mothers are HIV-positive (Ohto 1994; Zanetti 1995; Sabatino 1996; Tovo 1997; Granovsky 1998; Resti 1998; Thomas 1998b; Conte 2000). When these data are analyzed together, the average rate of vertical HCV transmission appears to be approximately 5%. Studies have demonstrated that rates of vertical transmission are dependent upon five factors: 1) presence or absence of HCV RNA in the mother; 2) high or low HCV viral load; 3) HIV status of the mother; 4) vaginal vs. caesarean delivery; and 5) breast vs. bottle feeding.

The only consistent factor found in studies is that vertical transmission does not occur if the mother is HCV RNA-negative at time of birth. In 20 perinatal HCV transmission studies analyzed by Dore and colleagues, none of the 735 aggregate HCVab+ but HCV RNA-negative women gave birth to an HCV-infected infant (Dore 1997). Some studies have documented a decreased incidence of vertical transmission from mothers with low HCV viral load (HCV RNA levels differ among studies). Other studies, however, have not found this correlation to be significant.

Mother's HCV RNA Level and its Correlation with Transmission of HCV to her Newborn: Conflicting Results

HCV RNA in transmitting mothers (copies/mL)	HCV RNA in non-transmitting mothers (copies/mL)	P	Study
1,000,000	15,000	<0.001	Ohto 1994
>2,000,000	<1,000,000	<0.001	Lin 1994
~1,000,000	~670,000	NS	Zanetti 1995
2,000,000	350,000	<0.001	Thomas 1998b
380,000	240,000	NS	Resti 1998
>1,000,000	<1,000,000	0.02	Mast 1999
2,150,306	2,038,375	NS	Conte 2000

There is considerable controversy as to whether the rate of HCV vertical transmission is higher when the mother is also HIV-positive. Many studies have been conducted solely in coinfected pregnant women and others in HCV-positve women with and without HIV. One of the most provocative findings comes from Zanetti and colleagues, a 1995 Italian study which included 116 HCV-positive women -- 22 of whom were coinfected with HIV. Of the 22 coinfected women, 18 had detectable HCV RNA. None of the infants born to 92 HIV-negative women acquired HCV, but 8 of the 22 (36%) infants born to coinfected mothers acquired HCV. While the eight mothers who transmitted HCV had detectable HCV RNA, there was no significant difference in HCV RNA levels between them and the other ten coinfected HCV RNA-positive women (Zanetti 1995).

Another Italian study of 245 infants found the incidence of HCV vertical transmission higher in coinfected mothers. Overall, 28 (11.4%) of the 245 infants acquired HCV: 3 of 80 (3.7%) whose mothers had HCV infection alone vs. 25 of 165 (15.1%) whose mothers were coinfected ($P<0.01$) (Tovo 1997).

In a study of solely coinfected mothers, Thomas and colleagues found that the risk of HCV infection was 3.2-fold greater if the infant also acquired HIV compared to HIV-uninfected

infants (17.1% of 41 vs. 5.4% of 112, P=0.04). All HCV transmissions were from mothers with HCV RNA viral loads over 2,000,000 copies/mL (Thomas 1998b).

A mother's co-infection was found not to be a significant risk factor for transmitting HCV in a New York multicenter study conducted by Granovsky and colleagues (Granovsky 1998). Five of 73 (7%) coinfected mothers transmitted HCV to their infants compared to 2 of 49 HCV+/HIV- mothers (P=0.7). There was also no significant difference in HCV viral load levels between transmitting and non-transmitting mothers. Lastly, an interesting finding about HIV and its possible enhancement of HCV transmission comes from the largest HCV vertical transmission study yet conducted. In a cohort of 370 anti-HCV-positive women, 15 (4.0%) were coinfected with HIV but did not transmit HCV to their infants. All of the coinfected women were receiving HIV antiretroviral therapy during their pregnancy, and investigators believe that reducing HIV-related immunosuppression may have affected HCV titers and the consequent likelihood of HCV transmission (Conte 2000).

A handful of studies have documented modest increases in the rate of HCV vertical transmission to infants delivered vaginally rather than by caesarean section (Tovo 1997; Granovsky 1998). However, larger studies with more patients have not observed any differences due to mode of delivery (Resti 1998; Mast 1999; Conte 2000). HCV transmission through breast feeding has not been considered a route likely source of infection for infants (Kumar 1998). In the vast majority of studies that evaluated breast feeding in infants born to HCV-positive women, no difference has been observed between bottle and breast feeding (Resti 1998; Tovo 1997; Mast 1999; Conte 2000). In fact, the CDC and the American Academy of Pediatrics do not feel that there is a risk from either breast feeding or vaginal delivery and have chosen not to recommend caesarean section or bottle feeding to HCV-infected mothers without HIV (CDC 1998).

Finally, no diagnostic screening criteria for perinatal HCV infection currently exist. Many studies have theorized about the optimal time to determine the infection status of an infant because various patterns have been observed in both infected and uninfected infants of HCV-positive mothers. For example, Conte and colleagues documented that the rate of HCV-positivity at birth for 366 newborns was 100%, but decreased to 90%, 63%, 16%, and 9% after 4, 8, 12, and 18 months respectively (Conte 2000). HCV RNA was detectable in 18 (4.9%) infants at birth, but 16 became negative by month four, and 6 infants who tested negative at birth became positive at month four. With similar findings from a recent CDC-sponsored study, Mast and colleagues concluded that "anti-HCV testing may not be a reliable marker of perinatal HCV infection until the infant is 2 years of age" (Mast 1999).

There appear to be as many knowns as unknowns with regard to HCV vertical transmission and the exact prognostic factors which lead to infection. According to Johns Hopkins' David Thomas:

> Without a randomized clinical trial, perinatal transmission cofactors will be difficult to evaluate conclusively. Even multiple consistent results from observational studies could be misleading. . . . The most conclusive randomized trial would have to include more than 800 mother-infant pairs to detect a twofold increase in transmission with 80% power. (Thomas 1998a)

Sexual Transmission

Is HCV sexually transmissable? For the past 11 years, this question has been widely studied and heavily debated among researchers from Atlanta to Australia. Miriam Alter and colleagues in a 1989 JAMA paper reported the first study to suggest that heterosexual transmission may play an important role in the spread of NANB hepatitis (Alter 1989). In this study, of 140 patients with HCV, 64 patients (46%) had no commonly recognized percutaneous risk factors; 7 (11%) had had multiple sexual partners and were believed to have contracted HCV through sex. Since then, there have been at least 50 articles published (not to mention scads of letters to the editors) in major hepatology, virology, and HIV-related peer-reviewed medical journals which have looked at HCV sexual transmission among the general population, hemophiliacs, heterosexuals, homosexuals, people with HIV and STDs, and sex workers.

Heterosexuals in Long-term Monogamous Relationships

Sexual transmission of HCV between heterosexual couples in long-term monogamous relationships who have no identifiable percutaneous risk factors (or after stratifying for such factors) appears to be quite infrequent. Gordon and colleagues reported that 2 of 42 (4.8%) heterosexual adults who were in stable sexual relationships with an HCV-infected partner developed HCV (Gordon 1992). Since one of the individuals had a risk factor for HCV, only 1 of 42 individuals (2.4%: 95% CI, 0.6-12.9%) was thought to have been infected through sex. Osmond and colleagues found the incidence of HCV to be high in their cohort of 170 men and 170 women in sexual partnerships: 31 (18%) of the women and 56 (33%) of the 170 men tested anti-HCV-positive (Osmond 1993b). Sexual transmission was not demonstrated because IV drug use, a history of a blood transfusion, or hemophilia treatment was associated with all but 2 of 87 HCV infections. No HCV transmissions were documented in a study of 94 husbands whose spouses all contracted HCV from contaminated anti-D immunoglobulin (Meisel 1995) nor in an Australian study which tested 50 heterosexual partners of HCV viremic individuals (Brester 1993). In Asian countries, however, higher rates of sexual transmission in married heterosexual couples have been reported, ranging from 8.8 to 28% (Chang 1994; Nakashima 1995; Chayama 1995).

Two large studies looking at the sexual transmission among female sex partners of HCV-infected hemophiliac males documented a low transmission rate. Eyster and colleagues and Brettler and colleagues found a sexual transmission rate of 2.6% and 2.7%, respectively (Eyster 1991; Brettler 1992).

In an elegant, high-tech study, Zylberberg and colleagues conducted genotypic, sequence, and phylogenetic analyses on 24 anti-HCV-positive couples to ascertain if they harbored the same strain of virus (Zylberberg 1999). The mean duration of the partnership was 12 years (range 1 to 36). Serum HCV RNA was detected in both partners in 18 (75%) of the couples and in only one partner in the other 6 (25%) couples. In the 18 couples who had detectable HCV RNA in both spouses, 11 of 18 (61%) had the same genotype while 7 of 18 (39%) did not. Phylogenetic analysis was conducted in 7 of the 12 genetically concordant couples. In three couples, HCV strains differed by 1 to 3 nucleotides with a sequence

similarity of 98% (evolutionary distance 0.065) suggesting that these spouses were infected by a common source. The other four couples differed by 4 to 15 nucleotides (evolutionary distance 0.0129) and thus their strains were considered unrelated. Sexual transmission of HCV was, however, ruled out in the three matched couples because all six spouses had at least one identifiable parental risk factor.

Sex Workers

A small number of studies, mostly outside the U.S., have been conducted among sex workers to ascertain if they are at higher risk for HCV transmission. Wu and colleagues studied 622 sex workers in Taiwan for anti-HCV antibodies and risk factors of transmission (Wu 1993). Seventy- four (12%) of the women were anti-HCV-positive and 60 (~10%) were HCV RNA-positive. In a multivariate analysis, history of paid sex for longer than six months and blood transfusion were positively associated with anti-HCV ($P<0.001$). Less than 20% of the HCV-infected sex workers had undergone a blood transfusion. Lissen and colleagues tested 310 Spanish female sex workers and 88 of their clients for anti-HCV (Lissen 1993). All denied prior transfusion or intravenous drug use. The prevalence of anti-HCV by ELISA, confirmed by a RIBA-2, was 6.4% among the sex workers and 6.8% among the clients. In contrast to these two studies, a very low rate of HCV positivity was reported in a study of Peruvian sex workers (Hymans 1993). Of 966 sex workers tested, only 7 (0.7%) had antibodies to HCV.

Homosexuals, People with HIV and STDs, and Sex Partners of IDUs

The prevalence of HCV appears to be substantially higher in homosexuals (men who have sex with men [MSM]), and people with HIV and STDs, than in the general population. Below is an analysis of 16 studies, most in high-risk populations, which document either sexual transmission or an infectious disease as a risk factor for HCV.

Sexual Transmission or an Infectious Disease as a Risk Factor for HCV					
Risk Group	Country	N	N (%) HCV+	Sexual and/or ID Risk Factor/s (Multivariate Analysis) Controlling for or Besides IV/BT	Study
MSM	US	926	15 (1.6%)	HAV	Donahue 1991
STD Clinic (MSM & HET)	UK	MSM 275 HET 771	19 (6.9%) 8 (1.0%)	HIV+, HBV+, and lifetime number of STDs (MSM only)	Tedder 1991

Female (F) sex partners of male (M) hemophiliacs	US	F 234 M 231	5 (2.6%)	Sex with an HCV+/HIV+ M: 3% HCV+ for sex with HIV+/HCV+ M vs. 0% with HIV-/HCV+ M	Eyster 1991^
MSM	US	735	34 (4.6%)	> 50 sex partners/year > 25 oral receptive partners per year	Osmond 1993
MSM, prostitutes, & HET partners of an HCV+ person	Spain	MSM 168 HET 147	7 (4.2%) 11 (7.4%)	Sex with HCV+/HIV+ (9.2% vs. 4.1% for HET sex with HCV+/HIV+ vs. HCV+ only)	Lissen 1993^
Prostitutes	Taiwan	622	74 (12%)	History of paid sex > 6 months	Wu 1993
STD Clinic (MSM & HET)	US	1,257	122 (9.7%)	M = >29 years & lack of condom use F = > 29 years & >1 sex partner prior month	Thomas 1994
STD Clinic (MSM & HET)	US	1,039: M 555 F 484	M 37 (7%) F 19 (4%)	Age >28; >24 lifetime sex partners; HIV+; Trichomonas infection; cigarette smoking. Omitting HIV+ showed MSM significant risk (p = 0.012)	Thomas 1995
MSM	Australia	1,038	79 (7.6%)	HIV+	Bodsworth 1996
Women with or at risk for HIV	US	296	123 (42%)	HIV+, sex with male IDU, history of gonorrhea, >35 years, not graduating high school	Hershow 1996
Volunteer blood donors	US (REDS)	862,398	3,126 (0.36%)	HTLV I or II, HBV or HIV (OR, 10.4)	Murphy 1996

HCV+ blood donors & HCV- controls	Canada	HCV+ 267 HCV- 1,068	N/A	Sex with an IDU (OR, 6.9)	Delage 1999
HCV+ blood donors & HCV- controls	US (REDS)	HCV+ 2,316 HCV- 2,316	N/A	Sex with an IDU (OR, 6.3)	Murphy 2000
MSM	Canada	120 HIV+ 112 HIV-	20 (8.6%): HIV+ 14% HIV- 2.7%	For the HIV+ men: Fisting (OR, 4.06) Rimming (trend)	Craib 2000
^ = subset analysis; BT = blood transfusion; MSM = men having sex with men; HET = heterosexual; STD = sexual transmitted disease; ID = Infectious disease					

In recent NEJM letters to the editor, CDC's Miriam Alter and Edward Murphy and colleagues from the NHLBI REDS sparred over the plausibility of HCV sexual transmission, citing selected studies to make their cases. Murphy started with, "[a] review of the literature suggests that sexual transmission of HCV is inefficient at best," and Alter countered that "results of both incidence and prevalence studies [show] that high-risk sexual behavior accounts for 15 to 20 percent of HCV infections in the United States." (Murphy 1999; MJ Alter 1999a).

Both make statements that are far too general and more important do not acknowledge that sex is not a defined act; it means different things to different people, and sexual practices can and do differ widely from household to household. These limitations (i.e., lack of detailing sexual acts or high-risk behavior) are common in a majority of studies reviewed. While some studies document that sleeping with an HIV-positive or HBV-positive individual is a risk factor for transmission, we don't know what was done in bed (if it was in a bed) that created the extra risk. Too often, "high-risk sexual behavior" and "sexual promiscuity" are not defined, nor are we privy to whether condoms were used. Thus, it is the particular sexual act (e.g., insertive vaginal or anal intercourse, oral sex, anal fisting, etc.) that needs to be explored for its risk of HCV transmission. Murphy's belief that sexual transmission is "inefficient at best" is surprising since it contradicts his 1996 JAMA and 2000 Hepatology papers on risk factors for HCV transmission in the REDS cohort, which document that HIV and HBV, and sex with an IDU, respectively, are risk factors in multivariate analyses (Murphy 1996, 2000).

Murphy's argument against sexual transmission -- even in homosexuals -- is weakly supported by a single review article, which fails to note that most studies rejecting the risk of sexual transmission were too small and underpowered to detect such risks (MacDonald 1996). According to Donahue and colleagues, who documented a 1.6% incidence rate of HCV in a cohort of 926 homosexuals, "the small number of HCV-seropositive subjects may have limited the power to identify risk factors for infection" (Donahue 1991). Likewise, Buchbinder aknowledged that the small sample size of her 1994 study (Buchbinder 1994) may have limited its power to find sexual transmission as a risk factor in the multivariate analysis, even though numerous sex acts were identified in the univariate analysis (Susan Buchbinder, personal communication, 2000).

It is not surprising that the risk of HCV sexual transmission appears greater for homosexuals than for heterosexuals. From HIV studies, we have excellent data documenting that the risk of transmitting HIV is greater for homosexuals than heterosexuals, for women from men than for men from women, and for anal than vaginal intercourse (Padian 1991; Kingsley 1990). Moreover, specific sex acts as well as the physical condition of an individual play major roles in establishing risk. For example, Moss and colleagues in 1987 documented that douching before anal sex (vs. not douching) was independently associated with HIV seropositivity (OR, 2.2-2.8) (Moss 1987). Chmiel and colleagues from the Multicenter AIDS Cohort Study (MACS) examined numerous types of sexual behavior between homosexual men and found that, aside from unprotected receptive anal intercourse, "the factor most strongly associated with prevalent HIV infection according to a multiple logistic regression model was rectal trauma, a composite variable which included receptive anal fisting, enemas before sex, reporting of blood around the rectum, and the observation of scarring, fissures or fistulas on rectal examination (OR, 7.7)." (Chmiel 1987)

While such behaviors are physical symptoms and are not universal among all homosexual men, if one partner with HCV has penile sores or ulcers and the other partner has blood around the rectum, fistulas, or fissures, it is plausible that there will be blood-to-blood contact and possible HCV transmission. Documentation of specific risk factors like these is necessary in order to 1) elucidate various ways the virus might enter the body; and 2) define specific "high-risk behavior" so that individuals can be counseled about which sexual practices lower the risk -- no matter how small it might be -- of contracting HCV.

The CDC states that "data indicate overall that sexual transmission of HCV appears to occur, but that the virus is inefficiently spread through this manner." It does, however, call for further research into this controversial area:

> More data are needed to determine the risk for, and factors related to, transmission of HCV between long-term steady partners as well among persons with high-risk sexual practices, including whether other STDs promote transmission of HCV by influencing viral load or modifying mucosal barriers. (CDC 1998)

After this call for more data, it is interesting to see that the CDC in its Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection places both "long-term steady partners of HIV-positive persons" and "persons with a history of multiple sex partners or

sexually transmitted diseases" in the same category as "persons for whom routine HCV testing is of uncertain need [emphasis added]" (CDC 1998).

The CDC and the Infectious Disease Society of America took a more proactive stance in 1999, calling for HIV-infected individuals to be screened for HCV in its revised USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in People with Human Immunodeficiency Virus (CDC 1999). Acknowledging that many HIV-infected individuals are coinfected with HCV, the guidelines give a nod to the safer-sex practice of condom use:

Although the efficiency of sexual transmission of HCV remains controversial, safer-sexual practices should be encouraged, and barrier precautions (e.g., latex condoms) are recommended to reduce the exposure of sexually transmitted diseases. (CDC 1999)

Why did it take until 1999 for the CDC to issue such a recommendation? In 1993, University of California-San Francisco (UCSF) epidemiologist Dennis Osmond sounded a calm but serious warning, which appeared to fall on deaf ears:

Despite the infrequency of HCV sexual transmission, sexual behavior may still be an important mode of spread if the pool of asymptomatic but infectious carriers is large. Because HCV infection becomes chronic in a high proportion of cases and subclinical hepatitis may be common, there is reason to believe that this carrier pool could be large, and even a low level of sexual transmission may result in a substantial attributable risk. (Osmond 1993a)

A Warning for Veterans

A fascinating study was recently presented which infers that the rate of HCV infection in U.S. veterans is 10 times higher than in the general population, and that combat blood exposure is a highly significant risk factor for HCV transmission. Briggs and colleagues from Teresa Wright's group at the San Francisco Veterans Affairs Medical Center (SFVAMC) conducted a study with 791 veterans undergoing routine outpatient phlebotomy at the SFVAMC (Briggs 1999). Participants had their blood screened for anti-HCV positivity by EIA II, which was confirmed by Chiron bDNA. All were asked to answer a detailed questionnaire regarding sociodemographic characteristics and potential HCV risk factors. Of the 791 participants (95% male), 150 (19%) and 110 (13.9%) were anti-HCV-positive and HCV RNA-positive, respectively. The multivariate analysis below documents four significant risk factors, including the surprising finding that those exposed to blood during combat were 2.5 times more likely to develop HCV.

Risk Factors for HCV Infection in San Francisco Veterans: Multivariate Analysis

Risk Factor	Relative Risk	95% CI	P
IV drug use	24.74	8.17-74.86	<0.0001
Incarceration >48 hours	3.37	1.36-8.31	<0.0080

Blood transfusion <1992	2.23	0.90-5.53	<0.0820
Combat blood exposure	2.47	1.06-5.73	<0.0350
(Briggs 1999)			

Conclusion

The discovery of the HCV virus by molecular techniques and the development of an antibody assay in 1989 were the first steps in understanding and identifying the cause of liver disease in blood transfusion recipients. Since then, the sensitivity and specificity of the EIA has markedly improved, and the screening of blood donors has made the blood supply significantly safer (risk of 0.001% per unit transfused). In the U.S., approximately 2% of the population (four million people) are infected with HCV, and HCV appears to more common in Blacks and Hispanics. Internationally, the prevalence ranges from 0.1% to 5%, but in Egypt, it is estimated to be 25%. It is almost certain that blood-to-blood contact is the only way to transmit HCV. Intravenous drug use (IVDU) remains the main mode of transmission, with rates of infection ranging from 75% to 92% in various cohorts. Those engaging in IVDU should be tested for HCV and refrain from sharing syringes, cotton, and cooking equipment. The rate of perinatal transmission of HCV is approximately 5%, and the CDC does not feel that there is a risk from either breast feeding or vaginal delivery. The risk of transmitting HCV sexually is a controversial subject. In monogamous heterosexual couples, there appears to be little if no risk, yet in certain populations, including homosexuals and people with HIV or STDs, the risk appears to be 5-15%. Larger studies are needed to determine which sexual practices place individuals at increased risk of contracting HCV. Until then, individuals with "multiple sexual partners" engaging in "high-risk" sexual behavior should always use condoms.

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Pathogenesis, Viral Dynamics, & Immunologic Response of Hepatitis C Virus

By Jeffrey Schouten

Most people infected with hepatitis C virus (HCV) do not have any acute signs or symptoms of hepatitis. They usually remain unaware that they have been infected during the first 10-20 years, unless they have a blood test. They will usually be found to have some elevations of liver enzymes in their blood, as a result of leakage of these enzymes from damaged or dying liver cells. Specific blood tests can determine the presence of antibodies to HCV, or measure the blood level of HCV RNA, also know as viral load, by polymerase chain reaction (PCR). HCV RNA is detectable within a few days after infection, and antibodies usually become detectable within 45-90 days (Seeff 1995).

The precise mechanisms by which HCV infection causes liver damage are not known; however, there is strong evidence that a person's own immunologic response to HCV contributes significantly to this process. The process of inflammatory changes seen in the liver over time results in the formation of scar tissue -- fibrosis -- that leads to cirrhosis. Cirrhosis -- extensive scarring of or fibrotic tissue replacement in the normal liver -- is responsible for the life-threatening complications of HCV and hepatocellular carcinoma (liver cancer). Carlo Ferrari and colleagues write:

The final outcome of infections by viruses that cause chronic diseases is believed to depend mostly upon the rate of replication of the infecting virus and the capacity of the immune system to mount rapid, multispecific and efficient virus-specific responses to inhibit infection before the virus can devise strategies to evade immune surveillance. (Ferrari 1999)

HCV is a single-stranded RNA virus which does not integrate into the host's genetic material. HCV must constantly replicate to maintain its presence in the human body and is very efficient at replicating inside of human cells.

HCV Replication and Kinetics

HCV infection persists in 70-85% of people infected, despite evidence of "readily detectable, multispecific, humoral and cellular immune response directed against all the viral structural and nonstructural proteins" (Chang 1998). HCV replication has been detected in hepatocytes (liver cells) and in peripheral blood lymphocytes, but not in immunologically protected sites, such as the testes and brain (Chang 1998).

Laskus and colleagues searched for sites of HCV replication outside of the liver in HCV/HIV coinfected people (Laskus 1998). They found evidence for HCV replication in the lymph nodes, pancreas, adrenal glands, thyroid, bone marrow, and spleen in an autopsy study of eight people who were severely immunocompromised at the time of death. The amount of HCV produced from these sites appeared to be relatively low. The clinical significance of extrahepatic HCV is not fully understood, and it is difficult to definitively determine the presence of replication in the absence of an in vivo model. In a recent publication, Laskus documented evidence of HCV replication in peripheral blood cells (monocytes/macrophages, and T and B cells) in HCV/HIV coinfected patients. He suggests

that HCV may replicate in the same cells infected with HIV and that there may be direct interactions between the two viruses (Laskus 2000). These data, however, have yet to be confirmed.

HCV production on a daily basis can be very high. HCV production can be as high as 1 x 1012 virions (one trillion) per day (Neumann 1998). Average HCV RNA levels (viral load) in people coinfected with HIV have been reported to be as high as 16.8 million copies per milliliter (mL) (Mika 1999). The half-life of an HCV virus is about 2.7 days (Neumann 1998).

Thomas and colleagues studied HCV RNA levels in 969 HCV-infected people, 468 with HIV and 501 without (Thomas 2000). They found that factors associated with lower average HCV RNA levels in the HIV-negative group included younger age, ongoing hepatitis B infection, and the absence of needle sharing. In the HCV/HIV coinfected group, no differences in HCV RNA levels were correlated with age, race, gender, or alcohol or drug use:

Mean HCV RNA Level in Patients with and without HIV

Group	**Mean HCV**	**RNA Level**
Total	(N = 969)	9.3 million copies/mL
HIV-negative	(N = 501)	6.73 million copies/mL
HIV-positive	(N = 468)	7.19 million copies/mL
(Thomas 2000)		

When interferon alfa (IFN) therapy is given to people with HCV infection, there is a two-phase decay. There is an initial rapid decrease in HCV RNA, then a secondary, slower decay, or decrease. The initial decay, about a 1.5 log decrease in HCV RNA seen during the first 48 hours, is thought to represent the blockage of HCV production by IFN. The second, slower phase of decay is thought to represent the death of HCV-infected hepatocytes, or liver cells (Neumann 1998; Perelson 1999a; Yasui 1998).

In HIV/HCV coinfected individuals, HCV RNA levels are observed to increase after the second day of IFN treatment even though there was a rapid decrease the first day. One interpretation of this observation is that while HIV coinfection does not interfere with IFN's ability to reduce HCV production, HIV infection may interfere with the eradication of infected hepatocytes (Mika 1999). This hypothesis, however, is very speculative.

Comparative Viral Kinetics

	HIV	**HBV**	**HCV**
Half-life	< 6 Hours	24 Hours	3 Hours
Daily viral production	> 10 10	> 10 11	> 10 12
Perelson 1999a; Ramratnam 1999)			

Perelson noted that while HCV does not cause clinically significant liver disease for decades, it is still a very dynamic process, with tremendous daily viral production, in most HCV-infected people.

Daily dosing of IFN, or the use of experimental IFNs with longer half-lives, such as pegylated-interferons, has been suggested as a way to increase the efficacy of therapy for HCV, due to the very large number of virions produced each day and the rebound in production which occurs on day two after IFN therapy (Zeuzem 1999). (See "HCV Treatments" chapter.) The changes in HCV RNA levels after the first four weeks correlate with the chance of obtaining a sustained response to therapy (Walsh 1998). Thus, kinetics studies are not only of academic interest, but may help design more rational therapy and predict earlier who might benefit from continued therapy.

Immune Responses to HCV Infection

Studies have shown that neutralizing antibodies are produced during HCV infection, but they do not appear to be protective against re-infection in humans or in chimpanzees (Ferrari 1999). The more critical determinant of the outcome of HCV infection seems to be the cell-mediated immune response, or the T-cell (CD4) response. People who are able to spontaneously clear HCV from their body have evidence of strong T-cell responses. Conversely, people who are chronically infected with HCV do not appear to either mount a strong T-cell response early after HCV infection, or maintain an initial strong T-cell response to HCV antigens (Gerlach 1999). In Gerlach's study, the 20 people (52.6%) out of 38 studied who cleared HCV infection all had a strong and sustained antiviral T-cell response to HCV, while the people who became chronically infected either showed no initial T-cell response (12, 31.6%) or did not maintain an initial strong antiviral T-cell response (6, 15.8%).

Over time, however, in most people chronically infected with HCV, T-cell responses increase but are not able to clear HCV. Ferrari and colleagues write that:

More information about the immune events taking place within the inflamed liver is required to draw a more reliable picture of HCV pathogenesis and to create the ground for more effective strategies of prevention and treatment of HCV infection. (Ferrari 1999)

Another limitation of current research is the lack of necessary cell culture systems and animal models to study the many complex factors involved in the immunologic responses to HCV infection (Cerny 1999).

Possible Strategies for a Virus to Escape Immune Elimination

- Decrease its visibility to the immune system.
- Decrease the effectiveness of antiviral cytokines.
- Increase the resistance of infected cells to CTL-mediated killing.
- Infect immunologically privileged sites.
- Induce immunologic tolerance.
- Immunologic evasion.
  (Cerny 1999)

Generally neither HCV RNA levels nor alanine aminotransferase (ALT) levels (liver enzyme levels) correlate very well with the extent of liver damage seen on biopsy. Gretch and colleagues, however, have reported that replication of HCV in human liver tissue shows a significant correlation with the severity of HCV infection. They reported a very strong correlation with the percentage of human liver tissues cells infected with HCV in vitro, and the degree of hepatic inflammation (Gretch 1999). They suggest that the amount of damage to the liver may be a factor of the process of HCV replication, not merely the presence of HCV in the liver.

Arguments Supporting the Relevance of Immune-mediated Liver Cell Damage in HCV Infection

In primary HCV infection, liver cell damage correlates with the development of the host immune response -- not with infection and HCV viral replication.

Chronic HCV replication can occur without significant liver cell damage.

HCV infection of liver cells does not appear to kill the infected liver cells.

Immunosuppression of people with HCV infection results in transient improvement in liver function tests, despite a surge in HCV RNA levels.

Liver cell damage is associated with an inflammatory infiltrate, and liver-infiltrating HCV immune cells associated with areas of liver damage suggest a causative role.
(Cerny 1999)

HCV Eradication?

While HCV is an RNA virus, it is not a retrovirus; therefore, HCV does not incorporate its genetic code into the host cell's DNA. So if all infected liver cells, or hepatocytes, and any other cells in the body which are infected with HCV die -- and there are no free HCV virions around to infect new cells-then the person will no longer be infected with HCV (i.e., the infection will be eradicated). Some investigators believe that most people who remain without detectable HCV RNA six months after therapy have achieved eradication (i.e., they are cured). (See "HCV Treatments" chapter.) Approximately 15% of people acutely infected with HCV are able to achieve life-long eradication of HCV from their body by their immune response. (See "HCV Natural History" chapter.) Whether people are in fact cured will require longer follow-up; however, there is an important implication to achieving eradication. People can be re-infected with HCV after they have had the initial HCV infection eradicated; there is no life-long HCV immunity (Farci 1992).

Extrahepatic Manifestations of HCV

While the primary site of clinical infection with HCV is the liver, a significant number of people develop disease symptoms at sites other than the liver, referred to as extrahepatic manifestations of chronic HCV infection. A recent report reviewed sites of HCV infection in 1,604 patients infected with HCV; it found that 74% of people had at least one extrahepatic manifestation of HCV infection (Cacoub 1999). The most common manifestations were:

- Arthralgia (joint pains)
- Paresthesia (nerve sensation abnormalities)
- Myalgias (muscle pain)
- Pruritus (itching)
- Sicca syndrome (dry eyes, skin, and mouth)

The report also noted some laboratory abnormalities such as cryoglobulinemia (increase in a certain type of "cold" antibody in the blood), antinuclear antibodies, low thyroxine (thyroid enzyme) levels, and anti-smooth-muscle antibodies. A multivariate analysis demonstrated that the following factors were associated with an increased incidence of extrahepatic manifestations:

- Age
- Female gender
- Extensive liver fibrosis (scarring)

Another study reported that 38% (122/321) of people with HCV infection had at least one extrahepatic manifestation, including joint pains (19%), skin changes (17%), dry mucous membranes (12%), and sensory nerve changes (9%). Thus, the most common symptoms involved the joints and skin. HCV/HIV coinfection was associated with an increased incidence of low platelet counts (thrombocytopenia) and autoantibodies (antibodies against body tissues) (Cacoub 2000).

All of these symptoms and laboratory abnormalities are typically seen in people with autoimmune diseases, or people with diseases that are the result of their own immune system attacking components of their own body. This observation provides additional support to the belief that much of the damage observed due to HCV infection is actually a result of an overactive immune system, or an immune system that is mistakenly attacking components in the body as it attempts to attack HCV.

The pathogenesis, viral dynamics, and immunologic response of HCV remain incompletely understood. Reliable and efficient cell culture systems and a small-animal model are needed to better understand these areas. It is hoped that further advancement in this field will lead to novel therapeutic agents to treat and cure patients with HCV.

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Natural History, Clinical Manifestations, and Prognostic Indicators of Disease Progression and Survival of Hepatitis C Virus (HCV) Infection

By Michael Marco

> The most accurate means of determining the entire spectrum of outcomes of HCV infection would be to identify a large cohort at a time of initial infection; to select a carefully matched seronegative control group who, like the seropositive group, could be maintained under active surveillance for periods of 30 years or more; and to omit therapy that might alter outcome and hence modify natural history. Obviously, these conditions cannot be met and, therefore, the desired information may never be forthcoming.
>
> -- Leonard Seeff, The Natural History of Hepatitis C -- A Quandary

Introduction

Numerous HCV natural history studies have attempted to detail the course of HCV infection, yet most have been unable able to chart disease progression from initial infection to end-stage disease, and only one has more than 25 years of follow-up (Seeff 2000b). Long-term, accurate natural history data are needed to better understand the pathogenesis of the disease and to determine which patients need treatment now, which ones can wait for more effective treatment, and which ones will probably never need treatment.

Clinical Features and Outcome of Acute HCV

Acute HCV infection most often exhibits no clinical symptoms: 60% to 75% of individual are asymptomatic; 20% to 30% become jaundiced; and 10% to 20% have symptoms including fatigue, nausea, and vomiting (Dienstag 1983; Aach 1991; Koretz 1993). In those who develop jaundice, peak bilirubin levels are usually less than 12 mg/dl (mean: 8.4 mg/dl) and levels appear to resolve in less than four weeks (Esteban 1999). Fulminant hepatic failure with primary HCV infection is extremely rare.

Approximately 20% of newly individuals have symptoms that arise before the seroconversion to anti-HCV occurs (antibody-positive) (Koretz 1993). The average time from exposure to seroconversion is approximately 50 days, although it can be as long as nine months (Tremolada 1991; MJ Alter 1992).

During acute infection, a person's aminotransferase (ALT) levels (liver enzymes) rise to 200600 IU/I, but in 20% of cases, peak ALT levels exceed 1000 IU/l (Esteban 1999). There is often an episodic, fluctuating pattern of ALT levels during the first few months, where levels flare to a 10- to 15-fold increase. Approximately 25% of patients develop a sustained plateau pattern where ALT levels remain below 450 IU/l for many months. In others, ALT level can normalize (suggesting recovery), yet flare up again within months to years. This pattern is a tell-tale sign of chronic infection with HCV and indicates a need for ongoing

ALT monitoring (MJ Alter 1992; Esteban 1999). More than 12 months after acute infection, ALT levels will continue to be elevated in about 60% of individuals (Esteban 1998).

Continued normalization of ALT levels -- termed "biochemical recovery" -- does not always mean a loss of anti-HCV or absence of HCV RNA (MJ Alter 1992). Likewise, continued abnormal ALT levels with anti-HCV positivity does not necessarily mean that a person is chronically infected with HCV. Fifteen to twenty-five percent of acutely HCV-infected individuals will clear their infections (Shakil 1995). Complete resolution of HCV infection is defined as both the absence of HCV RNA in serum and a normalization of serum ALT level. Shakil and colleagues from the National Institutes of Health (NIH) documented the rate of chronic HCV, using PCR and bDNA assays, and histologic (liver cell) damage in 60 anti-HCV positive individuals with chronic hepatitis (Shakil 1995). Tabled below are the results of the 60 patients equally divided into three groups: group 1: normal ALT levels; group 2: elevated ALT levels less than twice the normal range; and group 3: levels more than twice the normal range.

HCV Virologic & Histologic Confirmation of 60 Anti-HCV Volunteer Blood Donors				
	Group I N=20	Group II N=20	Group III N=20	P
Baseline ALT	42 (13-88)	80 (47-125)	125 (40-308)	<.0001
Virology				
HCV RNA PCR+	13 (65%)	19 (95%)	19 (95)	0.0009
HCV RNA bDNA+	12 (60%)	18 (90%)	17 (75%)	0.091
Histology				0.018
Normal	3	0	0	
Nonspec. Changes	3	0	0	
Chronic Hepatitis				
Mild	8	16	9	

Moderate	6	3	9	
Severe	0	1	1	
Active Cirrhosis	0	0		
(Shakil 1995)				

The presence of viremia (HCV RNA in blood) in all groups did not correlate with age, route of transmission, or duration of infection. Nonetheless, those who were HCV RNA-negative were more likely to have persistently normal ALT levels (78%) compared to those who were HCV RNA-positive (20%). Likewise, most of those who were HCV RNA-negative had either normal liver histologic findings or only mild changes (Shakil 1995).

Some individuals (~15%) who test HCV RNA-positive during acute or post-acute HCV infection may eventually become undetectable and, conversely, some (~19%) who initially test HCV PCR-negative may become detectable at a later date. Villano and colleagues from Johns Hopkins studied HCV RNA patterns in 43 HCV seroconverters (documented by EIA-2 and RIBA-2) who were followed for 72 months (Villano 1999). Six (14%) patients had documented viral clearance (undetectable HCV RNA, <500 copies/mL) between one and two years; one patient was initially undetectable for HCV RNA and remained negative. Two of the patients who cleared virus had ~1 million copies/mL of virus. Factors associated with viral clearance were: white race (P = 0.004); jaundice (P = 0.003); and lower peak viral titers (P = 0.003).

The presence of HCV RNA did not always precede the development of antibodies: 48% had HCV RNA at their first seroconversion visit; 33% were HCV RNA-positive a median 3.8 months before seroconversion; and 19% were HCV RNA-detectable a median 15.3 months after estimated date of seroconversion. The fact that a person who may initially test qualitatively HCV RNA-negative (no detection of HVC in serum) but later become positive suggests that "in clinical practice, virologic outcome must be determined by long-term follow-up, not a single HCV RNA level" (Villano 1999).

One significant finding in this study deserves comment. Seventy-four percent of the anti-HCV-positive patients in this study (the majority with a history of intravenous drug use (IVDU)) had been evaluated by a physician during their seroconversion intervals, yet only a few were recognized as having HCV or were screened for it. In this case, one cannot say that hepatitis was not detected because of limited access to health care. Even though HCV does not present with severe symptoms, this routine failure to diagnosis HCV in patients known to be at high risk indicates a striking lack of awareness by health care providers about HCV and its epidemiology.

Chronic Infection

Data from various studies indicate that 75-85% of individuals with acute HCV infection will become chronically infected (MJ Alter 1992; Shakil 1995; Villano 1999). The reason for such a high rate of chronicity is not completely understood. Some studies suggest that HCV persistence is related to the high mutation rate of HCV and the continual turnover of complex viral quasispecies that are able to evade the immune response of the host (Tsai 1998; Ray 1999). Farci and colleagues from the University of Cagliari and Robert Purcell's NIH laboratory recently published data which suggest that resolution of acute hepatitis is associated with relative evolutionary stasis of quasispecies, but progression to chronicity is correlated with genetic evolution of HCV (Farci 2000).

Only 60% to 70% of chronically infected individuals will have persistent or fluctuating ALT elevations; the other 30% to 40% will have normal ALT levels throughout the course of their infection. Two studies, one by Shakil and colleagues, the other by Pastore and colleagues have documented that relatively low (13-135) or normal ALT levels during acute infection were prognostic indicators predicting loss of HCV infection (Pastore 1985; Shakil 1995). In at least four other natural history studies, however, ALT levels were not found to be predictive of clearance (Mattsson 1989; Esteban 1991; MJ Alter 1992; Villano 1999). Except for the Villano study mentioned above, which noted that whites had a higher rate of clearance than blacks (80% of the subjects were black), and a small Swedish study (N = 37) by Mattsson that documented an increased rate of clearance among patients under 30 years old, no other major natural history studies have found any prognostic factors for disease clearance (Mattsson 1989; Villano 1999). In 2000, it is still a guessing game as to who will develop chronic infection. According to Juan Ignacio Esteban, "No clinical, biochemical or virological feature can predict the outcome of infection in a given individual" (Esteban 1999).

A liver biopsy gives the most accurate information about the degree of liver injury associated with HCV infection. There are many complex and detailed staging and scoring systems for liver biopsies (e.g., Knodell score, METAVIR fibrosis score).

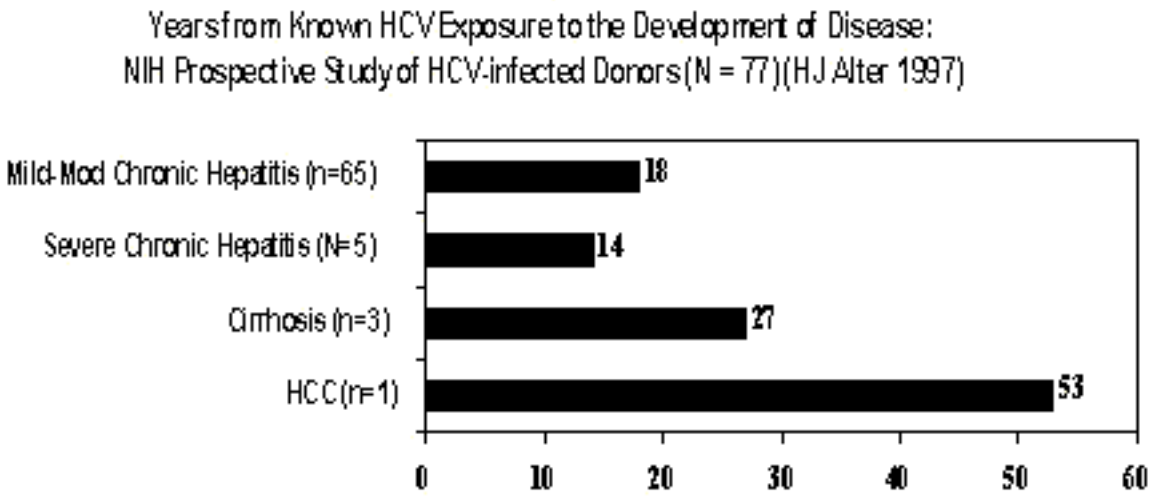
According to Leonard Seeff, natural history studies have used one of three evaluation strategies (Seeff 1997, 2000a):

Prospective studies starting with disease onset which have a low documentation of morbidity (symptoms, cirrhosis) and mortality (hepatic/liver failure, HCC). Follow-up tends to be short (8 to <20 years) and sample size is usually small.

Prospective studies of patients (usually older than 45 years of age) with already established chronic liver disease who have been referred to liver disease units/specialists. These tend to have shorter follow-up and referral bias with far sicker patients.

Retrospective/prospective (non-concurrent prospective) studies of recipients of HCV-contaminated immunoglobulin and transfused blood. These usually have an ~20 year follow-up period and contain matched non-hepatitis controls.

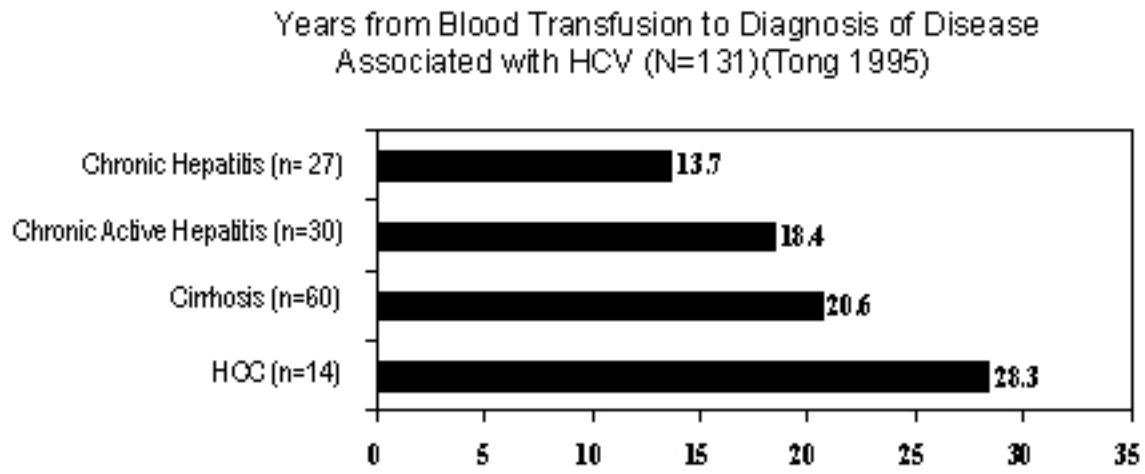
One of the most important prospective natural history studies, the NIH Prospective Study of HCV-Infected Donors, was recently published (HJ Alter 1997). It included 280 HCV RNA-positive blood donors followed for a median of 20 years. ALT levels were repeatedly normal in 17%; 45% had <2X the upper limit of normal; and 38% had a least one reading 5X the upper limit. Liver biopsies were performed on 81 of 280 patients, and a probable date of exposure could be ascertained in 74 of the 81. The chart below represents biopsy findings according to time from exposure:



Only 1.3% had histologic evidence of severe hepatitis and cirrhosis following a mean interval of 18 years from time of exposure. According to Harvey Alter, "Liver-related mortality or severe morbidity is less than 10% in the first two decades after infection." (Alter 1997)

Koretz and colleagues from UCLA documented a more progressive clinical course in their study of 80 recipients of HCV transfused blood who were followed for 14 years (Koretz 1993). After 16 years of known infection, 10% had HCV-related symptoms; 18-20% had biopsy-proven cirrhosis; 1.3% developed hepatocellular carcinoma (HCC; liver cancer); and 2.5% died of liver-related complication.

Cohort studies of chronic HCV patients referred to liver-oriented tertiary-care centers suggest progressive HCV disease. Tong and colleagues followed 131 patients with HCV for approximately 22 years: mean age at transfusion was 35 years, and at time of evaluation, the mean age was 57 years (Tong 1995). After about four years of follow-up, over 67% were experiencing HCV-related symptoms (specifically fatigue); 46% had biopsy-proven cirrhosis; 10.6% had developed HCC; and 15.3 % had died of liver-related deaths. The accompanying chart documents time to hepatic event:



Two significant retrospective natural history studies were recently published reporting the longest follow-up yet of well-characterized HCV infected cohorts (Kenny-Walsh 1999; Seeff 2000b). The first, by Kenny-Walsh and colleagues, documents the clinical course of HCV in a group of 376 HCV RNA-positive Irish women who had been infected during 19771978 with a batch of HCV-contaminated anti-D immune globulin (Kenny-Walsh 1999). The mean age of the women at time of infection was ~28 years, and after 17 years of living with HCV, the mean age of at screening/biopsy was 45 years. None had received any anti-HCV treatment. HCV-related symptoms, histologic grade of hepatic inflamation, and stage of fibrosis for the 363 women who underwent biopsies are documented below:

Symptoms and Histologic Findings in Irish Women ~17 Years Post HCV-infection			
Variable	No. of Women	ALT Level (U/liter)	
		Median	Range
Documented Symptoms (N=376)			
Reported >1 Symptoms	304 (81%)		
Fatigue	248 (66%)		
Arthralgia or Myalgia	143 (38%)		
Anxiety or Depression	60 (16%)		

Right-upper-quadrant Pain	23 (6%)		
Rashes	19 (6%)		
Histologic Findings (N=363)			
Grade of Inflammation			
0	7 (2%)	24	11-66
1-3	150 (41%)	37	10-61
4-8	190 (52%)	46	10-232
9-18	16 (4%)	80	34-381*
Stage of Fibrosis			
No Fibrosis	177 (49%)	35	10-198
Periorbital or Portal Fibrosis	124 (34%)	46	10-261
Portal-portal Bridging Fibrosis	36 (10%)	53	15-381
Portal-central Bridging	19 (5%)	100**	34-232
Probable or Definite Cirrhosis	7 (2%)	42	10-381
* Correlation between grade of inflamation and ALT levels (R=0.23, P<0.001) **Correlation between stage of fibrosis ALT levels (R=0.30, P<0.001) (Kenny-Walsh 1999)			

Compared to other studies, this study appears to document a slower progressive course of HCV infection. After 17 years of infection, no fibrosis was documented in nearly half of the women, and cirrhosis in only 2%. Another study from Germany of 152 women infected with HCV-contaminated RH0(D) immune globulin documented a similar clinical course (Muller 1996). After 15 years, none of the women were found to have chronic active hepatitis or cirrhosis. There are many speculations as to why disease in this cohort of

women was so indolent: 1) disease in women is less progressive than in men; confirmed by Poynard and colleagues (Poynard 1997); 2) patients infected at a younger age fare better than older ones; confirmed by Tong and colleagues as well as Poynard (Tong 1995; Poynard 1997); and 3) the small amount of the infecting dose of anti-D immune globulin (versus that of a blood transfusion) may have played a role (Kenny-Walsh 1999).

The 45-year HCV natural history study of 8,568 military recruits by Seeff and colleagues reports the earliest confirmed detection of HCV in the United States and has the longest follow-up of any study published to date (Seeff 2000b). Originally, 8,568 military recruits were tested for group A streptococcal infection and acute rheumatic fever between 1948 and 1954. After initial blood tests, samples were frozen and saved for 45 years. Seventeen (0.2%) individuals tested positive for HCV antibodies on EIA-3 and RIBA-3. While 17 HCV-positive patients followed in a natural history study may seem small, it's the HCV-negative control group of over 8,000 individuals (99% men) that makes this study important. Records tracking 45 years of liver abnormalities, disease, and death (using the National Death Index Plus service) as well as age, sex, race, chart review, and cause-specific mortality from death certificates were available from the Veterans Affairs' computer files.

A vast majority of the recruits were younger than 25 years of age at the original blood draw. Approximately 90%, 10%, and 0.5% were white, black and Asian, respectively. HCV infection in blacks was significantly higher than whites: 1.8% compared to 0.07% (RR, 25.9; CI, 8.4 to 80.0). The mean age of the surviving cohort, as of January 1997, was 64.8 years (95% were between 60 and 69 years of age). Eleven of the seventeen (65%) HCV-infected men were HCV RNA-positive; all but one had genotype 1b.

Death from All Causes & Liver-disease-related Mortality after 45 Years Follow-up in 8,568 Military Recruits

Event	HCV+ Group (N=17)	HCV-Group (N=8,551)	RR (95% CI) Ethnically Adjusted
Liver Disease	2 (11.8%)	205 (2.4%)	3.56 (0.94-13.52)
All Deaths	7 (41%)	2226 (26%)	1.48 (0.8-2.6)*
Mean Age at Death	56.5 years	54.2 years	NS
Liver Disease-related Death	1 (16.7%)	119/1890 (6.3%)	
Death from Liver	0	9 (0.5%)	

Cancer			
(Seeff 2000b)			

Of the seven deaths in the HCV-positive group, only one was due to liver disease. The fact that the event rate was so low in the HCV-positive group after four decades, and that there was little difference in mortality between the groups, leaves one to believe that HCV is a less progressive disease than is currently thought. According to Leonard Seeff, long-term natural history data have revealed that only 15% to 20% of HCV-infected persons will eventually develop progressive to potentially serious end-stage liver disease (namely cirrhosis) and that the remainder will die of causes other than liver disease (Seeff 2000a).

Prognostic Factors for Fibrosis Progression:
Good News for the Non-alcohol-imbibing Woman Infected with HCV Before She Was 40
A seminal natural history from France by Poynard and colleagues documents host factors, rather than virologic factors, as risks for fibrosis progression in untreated HCV-positive patients (Poynard 1997). Some 2,235 patients were selected from three well-characterized cohorts: Observatoire de l'Hépatite C (OBSVIRC); Cohorte Hépatite C Pitié-Salpêtrière (DOSVIRC); and the METAVIR. All patients underwent liver biopsy, and the METAVIR1 scoring system was used to grade the stage of fibrosis. Nine factors were assessed for effect on fibrosis progression: age at biopsy; estimated duration of infection; sex; age at infection; alcohol consumption; HCV genotype; HCV viremia; method of infection; and histologic activity grade. Fibrosis progression was defined as the ratio between fibrosis stage in METAVIR units and the estimated duration of infection. (For example, for a patient with stage 2 fibrosis who had been HCV-infected for eight years, the fibrosis progression rate would be 0.25 fibrosis units per year.)

The mean and median rate of fibrosis progression per year for the 1,157 patients whose duration of infection was known was 0.252 (95% CI, 0.227-0.277) and 0.131 (95% CI, 0.125-0.143), respectively. At this rate the median time to cirrhosis was estimated as 30 years (range: 28-32 years); 33% had a median time of 20 years and 31% will never progress or will not progress for at least 50 years. Out of the nine factors assessed, three had highly significantly correlation with disease progression: gender, alcohol consumption, and age at infection. Interestingly, amount of HCV RNA and viral genotype (i.e., 1b) did not correlate significantly with disease progression. (See "HCV Treatments" chapter, where both are significant prognostic factors for success of treatment.)

Multivariate Analysis of the Three Significant Risk Factors for Fibrosis Progression in 1,038 Patients			
Factor	**Relative**	**95% CI**	**for Fibrosis Progression in**

	Risk		**1,038 Patients**
Age at Infection (>40 years)	1.07	1.06-1.08	<0.0001
Male Sex	2.66	1.90-3.72	<0.0001
Alcohol Consumption (>50 grams/day)	1.49	1.18-3.03	<0.008
(Poynard 1997)			

Association between Rate of Fibrosis Progression and Age at Infection	
Age Group	Rate of Increase Fibrosis
31-40 Years vs. 21-40 Years	31%
41-50 Years vs. 31-41	45%
>50 Years vs. 41-50	67%
(Poynard 1997)	

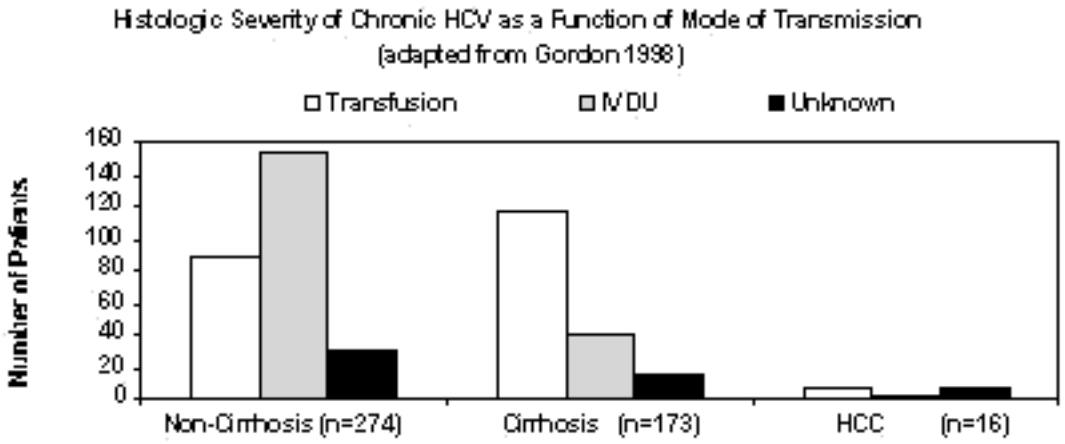
Varying prognostic factors predict a benign course of HCV for some and a severe one for others. A female infected before the age of 40 who drinks <50 grams (equals 5 glasses) of alcohol per day has an expected time to cirrhosis of 42 years compared to 15 years for a man infected after the age of 40 who drinks more than 50 grams of alcohol per day.

Selected Prognostic Factors for Disease Progression and Survival

Age (Tremolada 1992; Tong 1995; Fatovitch 1997; Poynard 1997; Neiderau 1998; Deuffic 1999); male gender (Poynard 1997; Deuffic 1999; Khan 2000); and increased alcohol intake (Donato 1997; Fattovitch 1997; Poynard 1997; Rudot-Thoraval 1997; Neiderau 1998; Wiley 1998) have been documented by many (but not all) as highly prognostic factors for HCV-related liver disease progression. However, other important prognostic factors for advanced disease progression have been less consistently documented in

published natural history studies. Mode of HCV transmission: Blood transfusion vs. IVDU vs. Sporadic Cases.

Two published studies have suggested that infection through blood transfusion (BT) (compared to infection via IVDU) is a highly significant prognostic factor for liver disease progression (Rudot-Thoraval 1997; Gordon 1998). Gordon and colleagues studied the clinical course of 627 chronically HCV-infected patients: 282 (45%) were BT recipients, 262 (42%) were infected via IVDU, and 83 (13%) were without known risk factors. The median estimated disease duration for all patients was 21 years (+/- 9.53 years) and the duration of follow-up ranged from 1 to 25 years. Liver histology was available on 463 patients. Cirrhosis was determined in 173/463 (37%): 118/173 (68%) were BT recipients; 40/173 (23%) were infected via IVDU (P<0.001). Below is a breakdown of those who had HCC, cirrhosis, or no cirrhosis:



Unlike the Poynard study (discussed above), in Gordon's patients, age or estimated disease duration did not predict risk of liver failure in the multivariate analysis (Poynard 1997; Gordon 1998). Rudot-Thoraval and colleagues from France also noted an increased prevalence of cirrhosis in BT patients in their survey of 6,664 chronic HCV patients (Rudot-Thoraval 1997).

Of 2,500 patients with known duration of HCV infection, the prevalence of cirrhosis for BT recipients was 22.8% compared to 5.8% for those infected via IVDU (P<0.02; OR = 0.61; 95% CI, 0.40-0.92).

"Sporadic cases" are HCV infections without identified risk factors. Fattovitch and colleagues from Italy noted that sporadic cases with compensated cirrhosis had poorer survival compared with those infected via BT or IVDU (Fattovitch 1997). Likewise, Khan and colleagues from Australia recently reported that sporadic cases were at significantly higher risk for cirrhosis, HCC, and liver transplantation or death (Khan 2000). The complete opposite was seen in a German HCV natural history study conducted by Hopf and colleagues (Hopf 1990). Finally, Poynard did not find any of these modes of transmission to be a significant prognostic factor in his study (Poynard 1997).

Abnormalities in Laboratory Values: Albumin and Bilirubin

In the 455 Australian HCV patients from the Khan study, serum albumin (a protein made by the liver that is responsible for maintaining fluid inside blood vessels) concentrations of <30 g/L at entry was associated with an 85% chance of liver-related complications at five years and a three-year mortality of 70% (Khan 2000). Gordon also noted that low serum albumin (3.2 g/L compared to 4.2 g/L) was an independent predictor of subsequent hepatic decompensation (P = 0.001; OR = 0.054; 95% CI, 0.030-0.099) (Gordon 1998). Similar findings were noted years earlier in two HCV natural history studies conducted by Fattovich and colleagues and Yano and colleagues (Yano 1996; Fattovich 1997). The deleterious effects resulting from low serum albumin levels in late-stage HCV patients prompted Hirsch and Wright to write in a Hepatology editorial:

End-stage disease from hepatitis C is one of the leading indications for liver transplantation in the United States. Currently, listing for transplantation requires significant abnormalities in at least 2 of 5 elements of the Child-Pugh [cirrhosis] classification. This may merit reassessment if the dramatic predictive value of the serum albumin alone can be validated in other large, prospective studies. (Hirsch 2000)

To a lesser extent, elevated bilirubin has been noted as a risk factor for HCV-related liver disease progression (Fattovitch 1997; Khan 2000). In their 1997 study of 384 Italians with cirrhosis, Fattovich and colleagues found that abnormally high bilirubin was a predictor of poorer survival (Fattovitch 1997). Those with bilirubin <17 mmo/L had five- and ten-year survival probabilities of 96% and 86% respectively, compared with 81% and 67% for those with bilirubin >17-<51 mmo/L (P = 0.0001).

Prolonged prothrombin time (decreased duration of blood coagulation) and decreased platelet count have been documented as significant predictors of disease progression in later-stage patients (Fatovitch 1997; Gordon 1998).

Coinfection with HAV, HBV, and HIV

(See "Hepatitis & HIV Coinfection" chapter for more details)

HCV patients who acquire HAV have been found to have a substantial risk for fulminant hepatic failure2 and death (Vento 1998). In an Italian HCV natural history study, 432 patients were tested thrice yearly for the development of HAV antibodies. Seventeen HCV patients (three with cirrhosis) subsequently acquired HAV infection. Ten of the patients had an uncomplicated course of HAV, but seven developed fulminant hepatic failure, and six died. There was no apparent difference in degree of baseline liver damage, yet the development of HAV posed a 41% chance of fulminant hepatitis and a 35% chance of death (Vento 1998).

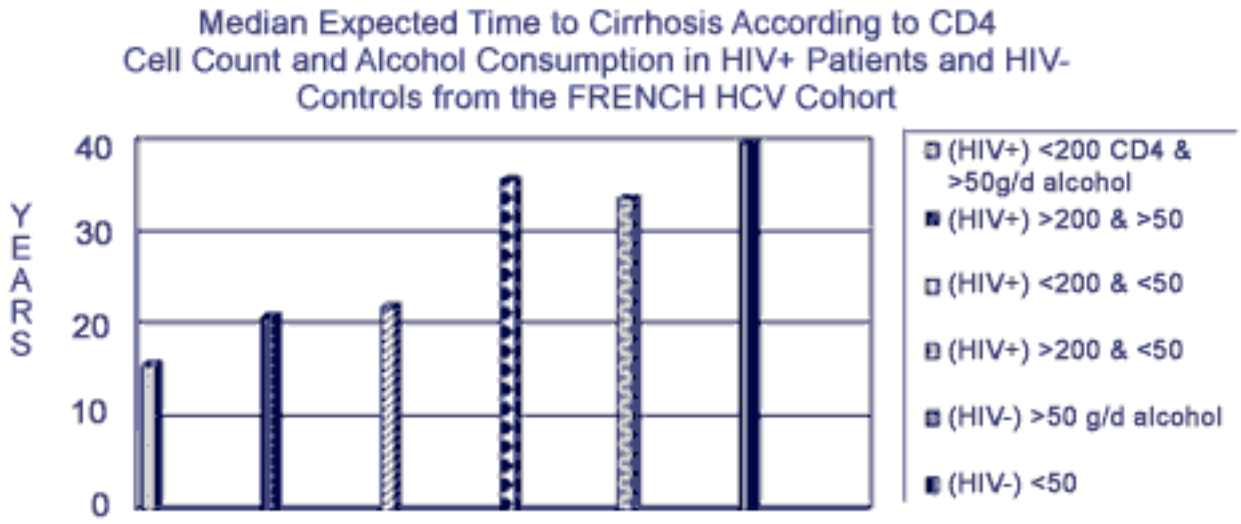
Vento concludes that all HCV-infected individuals should be vaccinated for HAV, saying, "Chronic carriers of HCV who are at risk for HAV infection should be vaccinated against HAV, since superinfection with this virus may place them at risk for severe, life-threatening acute liver damage" (Vento 1998). In a subsequent Lancet editorial, Marina Berenguer and

Teresa Wright agree that HAV vaccination may be warranted, but believe that Vento's results need confirmation and that a cost-benefit analysis is essential before implementing such a policy worldwide (Berenguer 1998).

HCV patients with HBV have been found to have an increased risk for cirrhosis (Roudot-Thoraval 1997; Cacciola 1999). Cacciola and colleagues from Italy tested for the presence of HBV DNA in a cohort of 200 chronically HCV-infected individuals. Sixty-six (33%) were found to have HBV sequences. Of these 66 patients, 22 (33%) had evidence of cirrhosis compared to 26 (19%) of 134 HCV-positive/HBV-negative patients (P = 0.04). This study confirmed the results of a French study of 5,786 histologically HCV-diagnosed patients (Roudot-Thoraval 1997). Cirrhosis at liver biopsy was found in 24.6% of patients positive for HBV surface antigens compared to 21.1% in those who were HBV-antigen-negative (P<0.001; OR = 1.99; 95% CI, 1.40-2.82).

Studies of people coinfected with HCV and HIV have reported that, while the progression of HIV disease is not changed by HCV, HCV infection progresses more rapidly in people with HIV. When matched for other variables, on average, people who are HIV-positive have higher levels of HCV RNA than HIV-negative people (Eyster 1993, 1994; Cribier 1995). It is important to note that a majority of natural history coinfection studies were conducted before the advent and widespread use of potent antiretroviral therapy. With control of HIV viremia and better immune status, the natural history of HCV in these patients will likely change. In immunocompetent HIV-positive individuals, HCV may replace certain opportunistic infections (i.e., Pneumocystis carinii pneumonia, mycobacterium avium complex and cytomegalovirus retinitis) as a leading cause of increased morbidity and mortality.

Benhamou and colleagues from Theiry Poynard's group in France have recently reported on fibrosis progression in their well-characterized coinfected DOSVIRC cohort (Benhamou 1999a, 1999b). Low CD4 count (<200 cells/mm3), alcohol consumption of more than 50 grams/day, and age at HCV infection (>25 years old) were shown to be associated with an increased liver fibrosis progression rate (Benhamou 1999b). In a linear progression model, there was little difference in time from infection to cirrhosis between the HCV+/HIV+ patients and the matched HCV+/HIV- groups if those with coinfection who had a T-cell count of >200 and drank <50 grams/day of alcohol. The accompanying chart documents time to cirrhosis:



Virologic Determinants

Quantitative HCV RNA levels do not appear to affect the clinical course of HCV-infected individuals who are naive to treatment. Lau and colleagues found no difference in serum HCV RNA levels between patients with chronic persistent hepatitis, chronic active hepatitis, or cirrhosis (Lau 1993). These finding were confirmed in larger natural history studies (Poynard 1997; DeMoliner 1998).

There is considerable debate as to whether certain HCV genotypes, especially 1b, put patients at increased risk for disease progression. Kabayashi and colleagues found that the deterioration of liver histology during a median 9.6 years of follow-up was more common in patients with genotype 1 (68%) -- namely 1b -- than in those with genotype 2 (41.7%) ($P<0.01$) (Kobayashi 1996). Likewise, an advanced stage of liver histology was more common in the genotype 1 patients (63%) compared to those with genotype 2 (38.9%) ($P<0.05$). An earlier, smaller study conducted in the United Kingdom also noted that those with genotype 1 had a far more progressive histologic disease than those with genotypes 2, 3, or 4 (Dusheiko 1994). However, difference in disease outcome according to genotype has not been verified in most treatment-naive natural history studies after 1996 (Poynard 1997; Serfaty 1997; Neiderau 1998; Khan 2000). Finally, in interviews conducted with leading hepatology researchers and clinicians, none believe that genotype independently has an effect on the natural history of hepatitis in patients naive to therapy (see "Current Opinions and Controversies" chapter).

The METAVIR scoring system grades the stage of fibrosis on a five point scale: 0 = no fibrosis; 1 = portal fibrosis without septa; 2 = few septa; 3 = numerous septa without cirrhosis; 4 = cirrhosis (The METAVIR Cooperative Group 1994). Histologic activity (intensity of necroinflammatory lesion) is graded on a four point scale: A0 = no histologic activity; A1 = mild activity; A2 = moderate activity; A3= severe activity.

Fulminant hepatic failure is the development of severe liver injury with hepatic encephalopathy (HE). HE is a condition where the brain function is impaired by the presence of toxic substances, absorbed from the colon, which are normally removed and detoxified by the liver.

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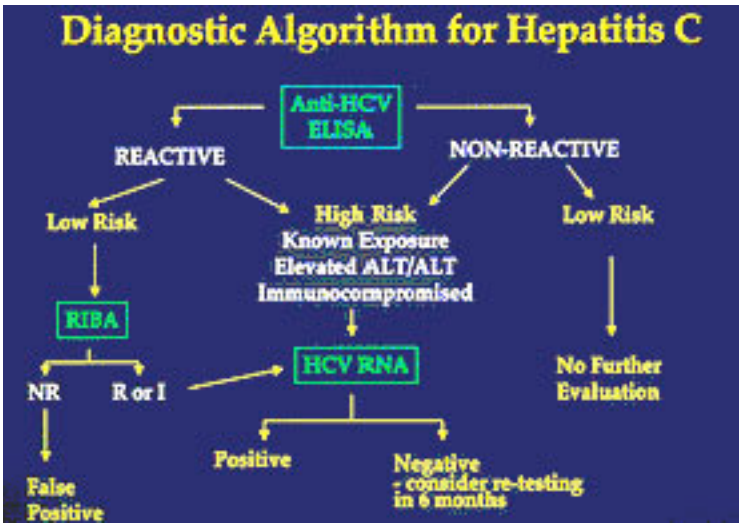
Diagnosis of Hepatitis C Virus (HCV)1 Infection

By Michael Marco

HCV diagnostic assays (tests) are important for four specific reasons: 1) to protect the blood supply; 2) to diagnose if an individual is acutely infected with HCV; 3) to determine if an individual is a chronic carrier; and 4) to evaluate the effect of anti-HCV therapies. There are currently three types of tests used for detection of HCV infection and quantification of virus: HCV enzyme immunoassay (EIA-2 and EIA-3); reverse immunoblot assay (RIBA-2 and RIBA-3), and polymerase chain reaction (PCR). Nonetheless, biopsy of liver tissue is still the gold standard for assessing the seriousness of hepatic disease in an individual with chronic HCV infection.



(Courtesy Norah Terrault, M.D.)

HCV EIA, RIBA, and Qualitative HCV RNA PCR

For most people, the diagnosis of HCV exposure is confirmed by detecting the presence of HCV antibodies (anti-HCV) in serum. Sensitive enzyme immunoassay (EIA) tests are commercially available for detecting anti-HCV. Three generations of these assays have been marketed to date: EIA-1, EIA-2, and EIA-3. The HCV EIA uses recombinant viral proteins that recognize epitopes of portions of the core and other viral proteins.

EIA-1 was developed in 1989 by Kuo and colleagues (Kuo 1989). It was an important breakthrough despite suboptimal sensitivity: only about 7080% (Gretch 1997). In 1992, the much-improved EIA-2 was released, which recognized epitopes from the core (c22), NS3, and NS4 proteins. The newer test also offered much greater sensitivity and it remains the most commonly used assay -- outside blood donation centers -- for detecting anti-HCV. The newest HCV antibody assay, EIA-3, modified its NS3 and NS4 regions and now recognizes additional epitopes from the NS5 protein.

Performance Characteristics of HCV EIA Assays			
Assay	Sensitivity*	Low Prevalence** Population	High Prevalence** Population
EIA-1	7080%	3050%	7085%
EIA-2	9295%	5061%	8895%
EIA-3	97%	25%	NA

* Based upon detection of HCV RNA by PCR (Terrault 1999, based on Gretch 1997)
** Positive predictive value compared with RIBA

A major problem with the HCV EIA is the low positive predictive value and high false-positivity rate in low-prevalence populations (i.e., blood donors, those without known risk factors, or those with normal ALTs). In these populations, it is advised that a reactive (positive) HCV EIA be confirmed with a reverse immunoblot assay (RIBA-2 or -3), also known as a "Western blot." The newer RIBA assays detect antibodies to each of the HCV proteins (core, NS2 through 5) in a nitrocellular strip format.

Data from two studies have demonstrated that non-reactivity to RIBA-3 correlates well with an absence of HCV viremia (Uyttendaele 1994; Zein 1997). If, however, an individual's sample is found to be reactive or to have an indeterminate reaction to the RIBA, a qualitative2 HCV RNA reverse-transcription polymerase chain reaction (PCR) assay is recommended to establish the presence or absence of HCV viremia (Terrault 1999).

In a high-risk population (those with elevated ALTs or a risk factor such as history of injection drug use, multiple sexual partners, or blood transfusion before 1992), a reactive HCV EIA-2 or -3 is often sufficient to confirm HCV infection. The next logical step would be either a qualitative HCV RNA PCR to differentiate acute versus chronic infection or a quantitative2 HCV RNA PCR (to establish baseline viral load) if the individual is considering anti-HCV treatment. PCR may be indicated for immunocompromised individuals (transplant patients, those with chronic renal failure or HIV infection). These individuals are often unable to develop an adequate antibody response, and PCR (qualitative or quantitative) may be necessary to detect HCV (Terrault 1999). Likewise, there is an increased rate of false-positive anti-HCV reactions in people with HIV infection (Zylberberg 1996). The current United States Public Health Service and Infectious Disease Society of America (USPHS/IDSA) Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus recommends that positive screening antibody tests for HCV in people with HIV infection be confirmed with either the RIBA or HCV RNA PCR. Also, HIV-positive people with undetectable HCV antibodies, but evidence of unexplained chronic liver disease, should have an HCV RNA test performed (CDC 1999).

A qualitative HCV RNA PCR test is the best way to determine the presence of virus during the approximately two-month "window period" between HCV exposure and the presence of antibodies. HCV RNA is detectable by PCR within one to two weeks after exposure. Schreiber and colleagues conducted a study to accurately estimate the risk of transfusion-transmitted HIV, HTLV, HBV, and HCV from screened blood which was tested and determined antibody-negative (Schreiber 1996). Using data on 586,507 persons who had given blood more than once (a total of 2,318,356 blood donations), they calculated that the risk of a donor's being HCV RNA PCR- positive during the initial period before antibodies became detectable was 1 in 103,000 (range: 28,000288,000). They concluded that screening blood for HCV with PCR would reduce the window of vulnerability by an estimated 59 days, and that the relative risk could be reduced by an additional 77%.

In 1999, Roth and colleagues confirmed these results and also demonstrated that PCR was suitable for rapid blood screening, testing 3,000 samples in seven to eight hours (Roth 1999). The authors make a case for routine HCV PCR screening in the blood-bank setting on the basis of improved safety as well as improved availability, with quarantine times for fresh-frozen plasma being reduced from six months after antibody testing to three to four weeks after PCR testing.

HCV RNA PCR qualitative and quantitative assays have not yet been approved by the FDA.3 Nevertheless, they are widely used in clinical practice and in treatment studies. They have become increasingly sensitive with a lower limit of detection of 10 to 1,000 genomic equivalents/mL. The major drawbacks of HCV RNA PCR assays are the wide variability and lack of standardization. Many studies have documented great variability in the detection of positive reference samples by labs using "in-house" PCR kits and labs using commercially available assays (Damen 1996). In 1997, a World Health Organization (WHO) international standard was established for HCV RNA nucleic acid testing (NAT) assays. This standard is used primarily in Europe; the U.S. FDA is currently working on its own standard.

Additionally, qualitative PCR is also an important tool for defining response to anti-HCV treatment with interferon (IFN) monotherapy or in combination with ribavirin (RBV). Below is a table explaining its clinical use:

Defining Response to Treatment Using a Qualitative HCV RNA PCR Assay			
	Timing	HCV RNA Detected by PCR	HCV RNA Undetectable by PCR
Early Response	3 months for IFN	6 months for IFN/RBV	Low likelihood of response if treatment is continued
End of	At treatment end:	Non-	Responder, but relapse is

Treatment Response	6 months for genotype non-1; 12 months for genotype 1	responder	common (10-50%)
Sustained Response	6-12 mos after stopping treatment	Relapser	High likelihood of long-term durable response

(adapted from Terrault 1999)

HCV RNA PCR Quantitative Assays

HCV RNA PCR quantitative assays are used for two reasons: 1) To determine the amount of virus in an individual who is considering therapy; and 2) To observe the rate of decline of viral load during the first few weeks of treatment as a predictor of complete response (Zeuzem 1998). Although the amount of virus does not correlate with ALT levels (Ghany 1996; Zeuzem 1996) or liver histology (Lau 1993; Poynard 1997; De Moliner 1998), baseline viral loads have been shown to be a predictor of response to therapy (Davis 1997, 1998; Poynard 1998).

There are four commercially produced quantitative assays; however, the most sensitive assay, SuperQuant HCV assay, used in the interferon and ribavirin combination therapy registrational studies, is not yet commercially available. The table below, adapted from Terrault, is an analysis of all four assays based on limit of detection, units, and cost:

Overview of Quantitative HCV RNA PCR Assays			
HCV Assay	Lower Limit of Detection	Units	Cost
Quantiplex HCV 2.0 (Bayer Diagnostics)	200,000	Eq/mL	$266
Amplicor HCV Monitor (Roche Diagnostics)	10002000	Copies/mL	$268
SuperQuant HCV (National Genetics Institute)	100	Copies/mL	$250
NASBA	NA	Copies/mL	$100200

(Organon Tekinaka)			
(adapted from Terrault 1999)			

The Amplicor and Quantiplex assays use different types of amplification techniques to quantify viral RNA: the Amplicor uses target amplification of primers from most conserved region of the HCV genome (5' untranslated region [5'UTR]); and the Quantiplex uses signal amplification that captures and targets probes from the 5'UTR and core regions, amplifying the HCV RNA with synthetic, branched DNA oligonucleotides. Both have been compared in numerous studies (Gretch 1994; Tong 1998; Lunel 1999; Martinot-Peignoux 2000).

Martinot-Peignoux and colleagues recently published results from a study comparing three quantitative assays: Bayer's Quantiplex (bDNA) v2.0, Roche's new Cobas Amplicor HCV Monitor v2.0, and NGI's non-commercially available SuperQuant (Martinot-Peignoux 2000). Both the level and range of quantification were similar among the assays, and results correlated well among various HCV genotypes. The SuperQuant detected all 22 samples with fewer than two million copies of virus compared with 17 of 22 and 19 of 22 with the bDNA and COBAS assays, respectively ($P>0.05$). While the bDNA assay appears less likely to accurately detect low levels of virus, it is considered the best for obtaining high-end quantification values (i.e. >5 million copies) (Reichard 1998).

Because quantitative HCV RNA measurements are beneficial only for pretreatment evaluation and for on-treatment observation, the CDC has not recommended sequential HCV RNA monitoring for all patients (CDC1998).

HCV Genotype

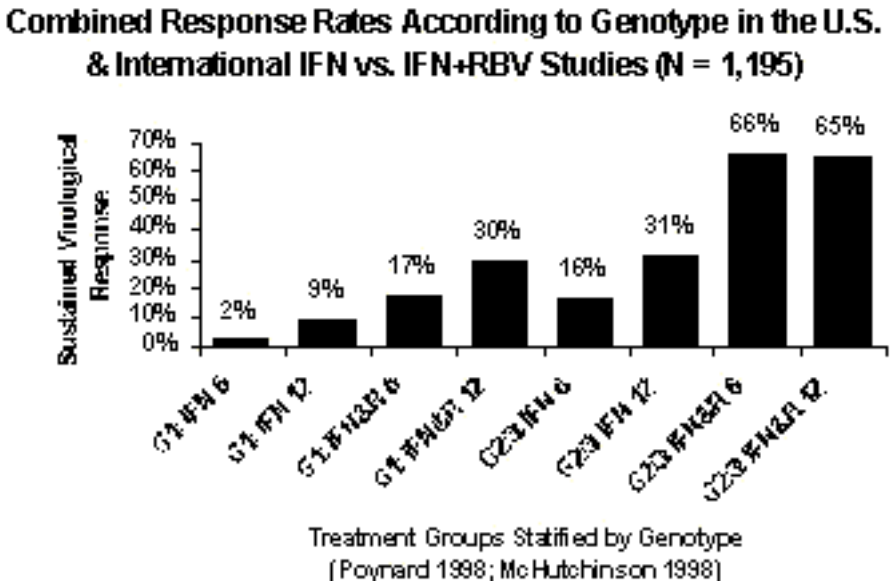
Not all individuals with HCV have identical viruses. Many different genetic variations (genotypes) of the virus exist. There are at least 7 distinct genotypes and at least 30 subtypes of HCV. The majority of HCV-positive individuals in the U.S. and Europe are infected with genotype 1; genotype 1a is more common in the U.S., and 1b is more common in Europe. Below is a breakdown of genotype prevalence from two recently published studies:

Prevalence of HCV Genotypes in the U.S. and Italy		
Genotype	NHANES III (MJ Alter 1999)	DIONYSOS (Bellentani 1999)
Genotype 1a	56.7%	4.3%

Genotype 1b	17%	42.0%
Genotype 2a	3.5%	24.0%
Genotype 2b	11.4%	0.6%
Genotype 2c		2.5%
Genotype 3a	7.4%	1.8%
Genotype 4	0.9%	
Genotype 6	3.2%	

Nucleotide sequencing and phylogenetic analysis of NS5B and E1 regions are considered the gold standard for determining HCV genotype, but cost prohibits these methods from being used clinically (Terrault 1999). The two commercial assays most commonly used are the INNO-LiPA HCV assay (Innogenetics, Zwijnaarde, Belgium) and the HCV serotyping assay (Abbott Laboratories).

Most natural history studies have demonstrated that HCV genotype in and of itself does not play a role in the clinical course of HCV. (For a detailed discussion, see the "Natural History of HCV" chapter.) Genotype can, however, be highly predictive of response to anti-HCV treatment. Recent clinical studies have demonstrated that sustained responses to treatment are significantly less likely for individuals with genotype 1 (Davis 1988, McHutchinson 1998; Poynard 1998). The accompanying chart details the sustained virologic response rates according to genotype for patients who received either 6 or 12 months of IFN alone or in combination with RBV in the U.S. and European IFN+RBV registrational studies:



The differences in the response rates between the genotype 1 group and the genotype 2/3 group -- regardless of ribavirin coadministration -- are dramatic.

Liver Biopsy

Liver biopsy is considered the gold standard for clinical assessment of individuals with chronic HCV. It is the only true way to determine the severity and activity of liver disease. Because HCV can be definitively confirmed with a qualitative HCV RNA PCR, a liver biopsy is most often reserved for those considering treatment in order to assess the grade and stage of hepatitis. A liver biopsy can also help rule out other forms of liver disease such as concurrent alcoholic liver disease, medication-induced liver injury, and iron overload.

A core liver biopsy is done in order to obtain intact tissue for a pathology reading. This procedure, with the use local anesthesia, involves the passage of a thin needle between the ribs through the skin to remove a tiny (1-inch long and 1/5-inch wide) piece of liver tissue. A liver biopsy is usually done in the hospital, and an individual may leave within three to six hours. The risk of complications from a liver biopsy -- primarily bleeding at the site of puncture into the liver -- is less than one percent. Approximately half of individuals have no pain from the biopsy, while others experience brief localized pain.

To avoid the risk of complications, some researchers have explored doing liver biopsies with imaging-guidance techniques such as ultrasonography (Papini 1991; Lindor 1996). Ultrasonography can aid in directing the needle away from large blood vessels, bile ducts, gallbladder, and colon, and thus potentially reduce complications. This procedure has gained some followers, yet it appears that most are skeptical about its necessity and concerned with the added cost (Smith 1999).

Recently, there has been a debate among clinicians about the need for liver biopsy in patients with HCV. Some believe that with the proper information from selected assays,

they can accurately determine the histologic grade and stage of a patient's disease. An interesting study investigating clinicians' predictions of patients' liver histologies by surrogate markers was presented at the 1999 Digestive Disease Week annual meeting. Romagnuolo and colleagues from Canada studied 45 patients referred to their hospital for treatment (Romagnuolo 1999). All clinicians' predictions were within one point of the actual grade and stage. Thirty-five (66%) of the patients' inflammatory scores and 40 (75%) of the fibrosis scores were exactly predicted, including four cases of cirrhosis. Age >40, spider nevi (abnormal blood vessels on the skin of the abdomen), organomegaly (abnormal enlargement of liver and/or spleen), white blood cell count <4,000, ALT >120, bilirubin >20, albumin <3.5, and ferritin (an iron-protein complex) >200 were predictors of more severe inflammation. The same variables (except ferritin and ALT) with the addition of platelets >150,000 and prothrombin time >1.2 were significant predictors of fibrosis.

The Knodell scoring system (used mostly in the U.S.) is an important, yet complicated, tool for documenting histologic activity. It is used to grade the level and extent of inflammation, necrosis, and fibrosis of a liver biopsy. Biopsy specimens are graded in four categories:

- Periportal +/- bridging hepatocellular necrosis I
- Intralobular degeneration and hepatocellular necrosis
- Portal inflammation
- Fibrosis

A numeric score for each category is assigned to each liver biopsy specimen, and the combined score of the four categories form the HAI (Histology Activity Index) score for that biopsy specimen. Note: The score goes from 1 to 3, omitting 2 intentionally.

Knodell Histology Activity Index (HAI)							
I	Score	II	Score	III	Score	IV	
Periportal +/- Bridging Hepatocellular Necrosis		Intralobular Degeneration and Hepatocellular Necrosis		Portal Inflammation		Fibrosis	Score
None	0	None	0	No Inflammation	0	No Fibrosis	0
Mild Piecemeal Necrosis	1	Mild (acidophilic bodies, ballooning degeneration	1	Mild (sprinkling of inflammatory cells in <1/3 of portal	1	Fibrous Portal Expansion	1

		+/- or scattered foci of hepatocellular necrosis in <1/3 of lobules or nodules)		tracts)			
Moderate Piecemeal Necrosis (involves <50% of circumference of most portal tracts)	3	Moderate (involvement of 1/3 to 2/3 of lobules or nodules)	3	Moderate (increased inflammatory cells in 1/3 to 2/3 of portal tracts)	3	Bridging Fibrosis (portal-portal-central linkage)	3
Marked Piecemeal Necrosis (involves > 50% of the circumference of most portal tracts)	4	Marked (involvement of >2/3 of lobules)	4	Marked (dense packing of inflammatory cells in >2/3 of portal tracts)	4	Cirrhosis	4
Moderate Pecemeal Necrosis Plus Bridging Necrosis	5						
Marked Piecemeal Plus Bridging Necrosis	6						
Multilobular Necrosis	10						
(Knodell 1991)							

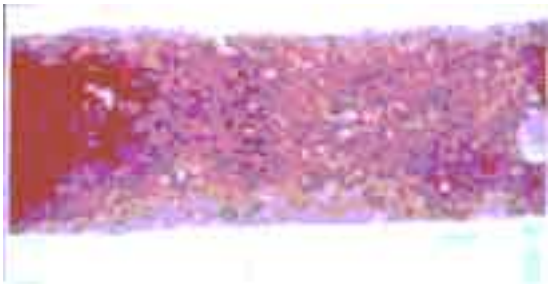
It is not crucial for individuals with HCV to know and memorize their HAI score. It can be useful, however, for them to understand the condition of their liver and to know the degree of inflammation, the stage of fibrosis, and if cirrhosis has occurred.

Fibrosis of the liver is the presence of scarring that results from the repair of hepatic tissue damage. In the case of HCV, the scarring is initiated by HCV-infected hepatocytes and the resultant inflammation. Liver fibrosis occurs slowly, first in the outer (portal) areas of the liver and then working its way in (bridging) to the central vein area.

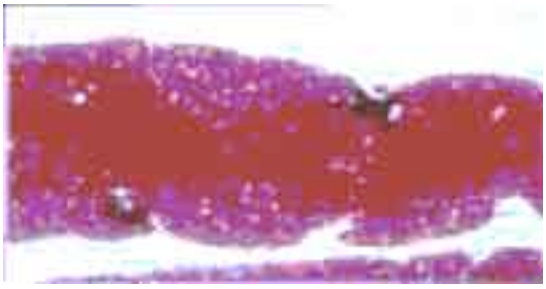
Extensive fibrosis and deterioration of the liver's cellular architecture is called cirrhosis. Cirrhosis results when most normal liver cells have been replaced by scar tissue. It can greatly interfere with the liver's ability to perform many of its usual functions, including the production of proteins and enzymes, the regulation of cholesterol and storage of energy, and the metabolism of drugs and toxins. Cirrhosis can lead to internal bleeding, kidney failure, mental confusion, fluid accumulation, infection, and coma.

Below are photographs of liver biopsies documenting various histologic stages of HCV:

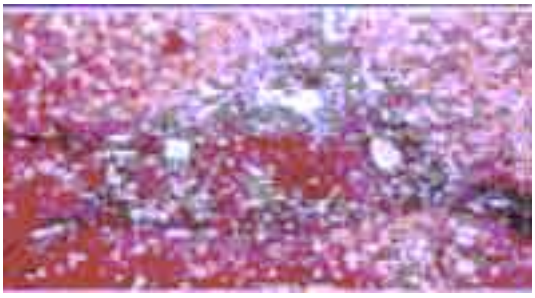
HCV Disease Progression



Normal



Mild Chronic Hepatitis



Moderate Chronic Hepatitis

Cirrhosis

(Courtesy Mark Sulkowski, M.D.)

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Much of this chapter has been adapted from Norah Terrault's printed syllabus and lecture, Viral Diagnostic Studies, AASLD, Postgraduate Course, Dallas, 11/5/99.

A qualitative PCR tells you whether virus exists. A quantitative PCR tells you how much virus exists.

In May 2000, Roche Molecular Systems was granted priority review by the FDA for its two experimental qualitative HCV RN.

Treatment of Hepatitis C Virus (HCV) Infection: The Interferon Story

By Michael Marco

> The irony, then, is that patients with the lowest likelihood of progression and who need therapy the least are precisely the ones who are most likely to respond and benefit most. In contrast, those who have features correlating with more progressive disease, who require therapy the most, are the ones least likely to respond and to benefit.
> -- JL Dienstag, The Natural History of Chronic Hepatitis C and What Should We Do About It?

> Current therapies are still unsatisfactory and should be limited to patients who have evidence of moderately severe or progressive disease.
> -- JH Hoofnagle, Therapy of Chronic Hepatitis C

Introduction

There are limited treatment options for people with HCV. For approximately 70% of HCV-infected individuals in the United States and Europe, currently approved treatments are seemingly ineffective (McHutchinson 1998; Poynard 1998). For the rest, however, treatment can result in what some people would consider a "cure." Interferon-alpha (IFN) was the gold standard of treatment for HCV for many years, and now IFN in combination with the nucleoside analog ribavirin is the regimen of choice. There are as many arguments to recommend starting treatment as there are to wait for safer and more effective ones.

In this chapter, I will analyze existing treatment data of FDA-approved therapies in order to examine questions of who should start, when to start, and when to stop anti-HCV therapy. If physicians treating HCV do not know all of this by heart, they should. It is imperative they be able to communicate this information so their patients can make informed decisions about when and if to start treatment. According to Willis Maddrey, "The appropriate education of the patient is both an obligation and an opportunity for the physician" (Maddrey 1999).

Endpoints: Criteria and Definitions

Before discussing results from treatment studies, it is important to first define the criteria used to establish response rates. Until recently, investigators used numerous terms and definitions to describe treatment response, and this lack of standardization makes it difficult to compare study results (Lindsay 1997).

A beneficial response to therapy has been based on three endpoints:

- Biochemical: Normalization of ALT levels (liver enzymes)
- Virologic: Lack of HCV RNA (undetectable (< 100 copies/mL))
- Histologic: Improvement in liver biopsy (> 2 Knodell HAI points)

They are measured at two separate time points:

- End of therapy response (ETR)
- Sustained response (SR): Six months after stopping therapy

IFN Monotherapy

Interferon is a naturally occurring protein secreted by mammalian cells. It has antiviral, anti- inflammatory and immunoregulatory properties (Borden 1981). Its exact mechanism of action against HCV is incompletely understood. (See the "HCV Virology" chapter for more information.)

In 1986, and before the HCV virus was identified (it was simply named non-A non-B hepatitis), Hoofnagle and colleagues at the National Institutes of Health (NIH) conducted the first study of IFN treatment for HCV (Hoofnagle 1986). Data from this and subsequent randomized controlled trials of IFN documented a reduction in ALT levels and improvement in liver histology. (There was no viral load monitoring since no one knew what virus was being treated.)

IFN was approved by the Food and Drug Administration (FDA) in 1991 for the treatment of chronic HCV at the dose of three million units (MU) subcutaneously (injection under the skin) three times a week (tiw) for six months. In 1997, the FDA granted marketing approval for IFN extended dosing of 12 to 24 months. IFN is also indicated for the treatment of hairy cell leukemia, AIDS-related Kaposi's sarcoma, chronic myelogenous leukemia (Roferon-A), malignant melanoma (Intron-A), follicular lymphoma (Intron-A), and condylomata acuminata (Intron-A) (PDR 2000).

Between 1986 and 2000, over 100 studies of IFN monotherapy for the treatment of HCV were conducted. Overall, a six-month course of IFN at 3 MU tiw has been shown to induce a biochemical end of therapy response (ETR) of 40-50% and sustained response (SR) of 15-20%. Virologic ETR is usually 30-40%, and the SR drops to 10-20% (NIH Consensus Panel 1997). Biochemical and virologic responses have usually been accompanied by histologic improvement (Poynard 1996; Marcellin 1997; Shiffman 1997).

While an SR is seen in ~20% of individuals on IFN monotherapy, these sustained responses are usually durable and considered by some as a "cure." Marcellin and colleagues studied 80 French HCV patients who had sustained a biochemical and virologic response to IFN monotherapy for at least 12 months (Marcellin 1997). Patient's serum and liver tissue samples underwent PCR analysis, ALT levels were measured, and liver biopsies were performed at least once over a six-year period. During a mean follow-up of four years (range: 1-7.6 years), 93% of patients had persistently normal ALT levels, 96% remained

undetectable, 62% had normal or nearly normal histologic findings, and liver HCV RNA was undetectable in all 27 patients tested. According to Marcellin:

The absence of detectable liver HCV RNA 1 to 5 years after treatment is consistent with the view that HCV infection may be cleared with interferon-alpha therapy in patients with chronic hepatitis C. (Marcellin 1997)

There has been considerable debate about the optimal dose and duration of IFN monotherapy. In the U.S. IFN is approved for treating HCV at the 3-MU dose; the 6-MU dose is indicated only for retreatment of IFN-relapsers (PDR 2000). In Europe, however, the 6 MU tiw dose is indicated for the first three months, followed by the 3 MU dose. Poynard and colleagues conducted a meta-analysis using 37 randomized controlled trials to evaluate the benefits of higher dose (6 MU vs. the standard 3 MU) and longer treatment duration of IFN monotherapy (12 months vs. 6 months) (Poynard 1996). Using only biochemical endpoints in the analysis, the ETR for the 6-MU dose was not statistically different from the 3-MU dose, but the 12-month course was shown to generate a 16% increase over the 6-month course (9% vs. 23%; $P<0.001$).

These data assisted a panel of expert international hepatologists at the NIH Consensus Development Conference in 1997 in recommending the dosage of 3 MU tiw for 12 months. An interim assessment at three months was recommended. If a patient's ALT level had not normalized and HCV RNA was still detectable, "interferon therapy should be stopped, because further treatment is unlikely to induce a response" (NIH Consensus Panel 1997). If either the ALT was normal or the HCV RNA was undetectable, continuation of treatment for the full 12 months was recommended.

The NIH Consensus Panel, which convened before the results of the combination IFN/ribavirin studies had been published, made the following judgments:

IFN therapy is indicated for chronic HCV in patients 18 to 60 years of age who have:

- a persistently abnormal ALT (greater than six months)
- a positive HCV RNA
- a liver biopsy demonstrating either portal or bridging fibrosis and at least a moderate degree of inflamation and necrosis.

Indication for IFN therapy is less clear for patients who:

- are under age 18 or over 60
- have compensated cirrhosis
- have milder histologic disease
- have acute hepatitis

IFN therapy is not indicated for patients with:

- decompensated cirrhosis
- mild disease (minimal histologic abnormalities)
- a persistently normal ALT level

IFN therapy is contraindicated for patients with:

- a history of major depressive illness
- active alcohol or illicit drug use
- cytopenia (more than one type of blood cell deficiency)
- hyperthyroidism (overactivity of the thyroid gland)
- renal transplantation
- autoimmune disease

Last, therapy should not be limited (forbidden) by:

- mode of HCV acquisition
- risk group
- HIV status
- HCV RNA level (viral load)
- genotype

There are many different commercially available interferons which have been evaluated in HCV studies: IFN alfa-2b (Intron A, Schering-Plough); IFN alfa-2a (Roferon-A, Hoffmann-La Roche); IFN alfa-n1 (Wellferon, Glaxo Wellcome); consensus interferon (Infergen, Amgen). According to the NIH Consensus Panel, "All forms of interferon appear to have similar efficacy in chronic hepatitis C" (NIH Consensus Panel 1997).

Combination Therapy: Interferon + Ribavirin

Ribavirin is a synthetic guanosine [nucleoside] analog which has in vitro activity against a range of RNA and DNA viruses (Patterson 1990). In monotherapy studies in patients with chronic HCV, ribavirin has been shown to decrease ALT levels, yet had no HCV antiviral activity (Bodenheimer 1997). Also tested in HIV antiviral studies, ribavirin monotherapy demonstrated no clinical antiviral activity (Roberts 1990); nonetheless, it has demonstrated profound synergistic effect with IFN in improving response rates in chronic HCV studies. Its exact mechanism of action, however, remains incompletely understood.

Combination IFN and ribavirin (IFN/RBV) was initially studied in pilot and phase I-II studies of patients who were either untreated or had experienced relapse; results suggested that IFN/RBV was more effective than IFN alone (Schvacz 1995; Schalm 1997; Reichard 1998).

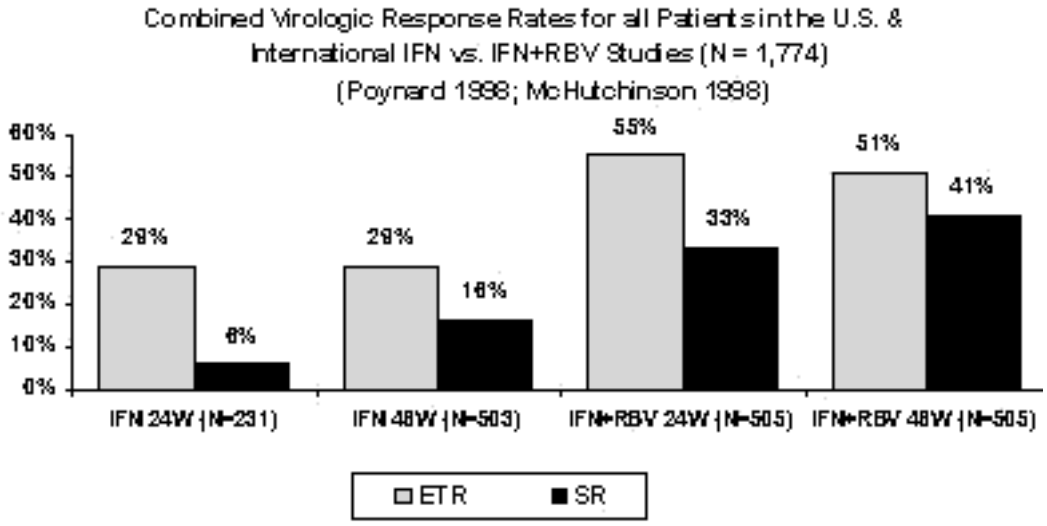
Two large, multicenter, randomized trials comparing IFN/RBV with IFN in untreated patients with chronic hepatitis C were conducted in the U.S., Canada, and Europe (McHutchinson 1998; Poynard 1998). The U.S. study conducted by McHutchinson and colleagues randomized 912 patients, and the international study by Poynard and colleagues randomized 832 patients. For discussion and presentation, results of these studies are usually combined because of the similarity of design, monitoring, endpoints, and virologic testing.

Patients were included in these studies if they had documented chronic HCV (both anti-HCV and HCV RNA in serum), raised ALT levels, compensated liver disease (non-cirrhotic), biopsy-proven chronic hepatitis, and no contraindication to therapy or other serious medical illnesses (i.e., decompensated cirrhosis, cytopenia, autoimmune disease). The U.S. study randomized patients to four treatment arms:

A. IFN (3 MU tiw) for 24 weeks
B. IFN (3 MU tiw) for 48 weeks
C. IFN (3 MU tiw) + RBV (1000 or 12001 mg/day) for 24 weeks
D. IFN (3 MU tiw) + RBV (1000 or 1200 mg/day) for 48 weeks

The international study randomized its patients to the equivalent of arms B, C, and D. Arm A (IFN monotherapy for 24 weeks) was not included.

The virologic end of treatment response (ETR) and sustained response (SR) for all 1,744 patients from both studies are listed in the charts below:



Virologic SR rates (primary endpoint = HCV RNA <100 copies/mL) were significantly better in the combination IFN/RBV arms than in the IFN monotherapy arms. Normalization of ALT levels (a secondary endpoint) closely mirrored virologic response rates. Normalization of ALT levels was associated with achievement of undetectable HCV viral loads. Likewise, the percentage of patients with documented histologic improvement (another secondary endpoint) was markedly better in patients in the combination treatment arms: IFN 24W = 44%; IFN 48W = 41%; IFN/RBV 24W = 57%; and IFN/RBV 48W = 61%.

Results of these studies suggest two things: 1) IFN/RBV combination therapy is superior to IFN monotherapy; and 2) the 1997 NIH Consensus Panel was correct in its recommendation that IFN monotherapy should be administered for 48 weeks rather than 24 weeks (NIH Consensus Panel 1997).

As impressive as these results appear, a majority of HCV patients on combination therapy do not have a 50% chance of clearing virus. An analysis of factors predictive of response to therapy sheds light on which patients do well and which fair poorly on IFN/RBV therapy.

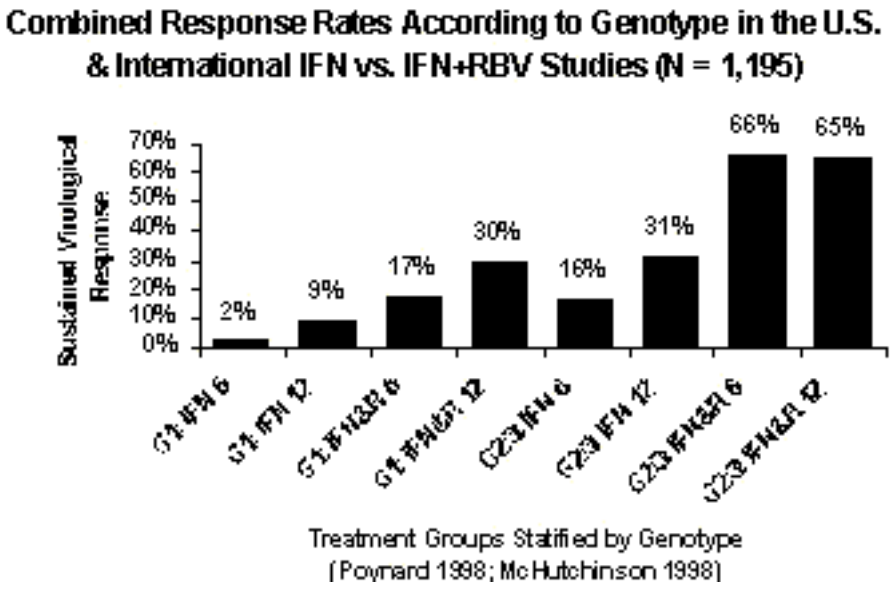
Factors Predictive of a Response to Therapy

Host Factors

Using logistic regression analysis, three host factors were found to be independent positive predictors of SR: 1) female sex; 2) lesser degree of fibrosis on baseline liver biopsy; and 3) age < 40 years (observed only in the international study). Note: Patients with alcohol dependency were excluded from the studies.

Viral Factors

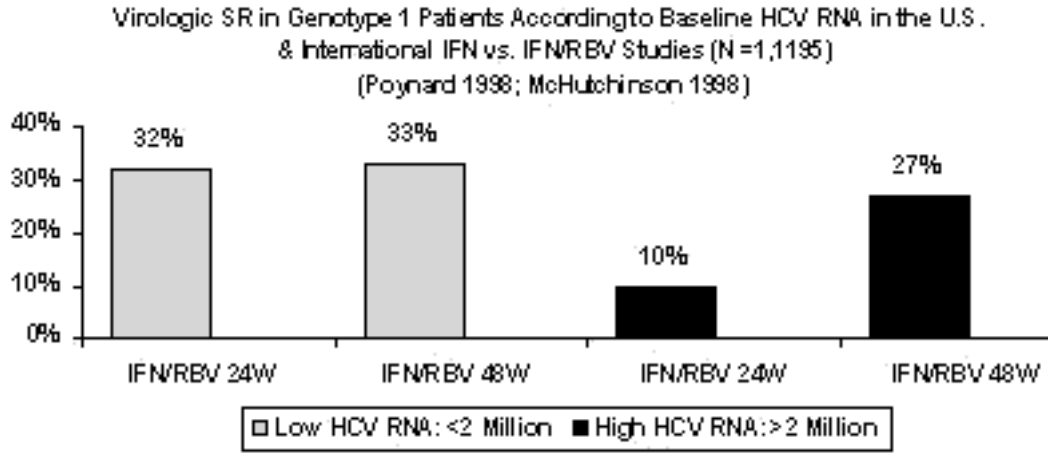
Two viral features, HCV RNA copy number and HCV genotype, were overwhelmingly the strongest predictors of response. Patients with genotype 2 or 3 had approximately double the virologic response rate of those with genotype 1. The chart below details virologic SR rates according to genotypes2:



Thus, while genotype 1 accounts for about 75% of U.S. HCV infections (MJ Alter 1999), and has no prognostic value in HCV natural history if untreated (Poynard 1997; Khan 2000), it is the strongest prognostic indicator for successful response to therapy. The 51-55% SR virologic response rate seen for all study patients immediately drops more than 20% to a disappointing 30% SR rate if only persons with genotype 1 are analyzed. Conversely, two-thirds of the genotype 2/ 3 patients successfully achieve an SR. It is quite possible that some individuals with genotype 1 are resistant to IFN.

Baseline HCV RNA was also identified as a strong predictor of a virologic SR. While HCV RNA is a strong predictor of treatment outcome, it has no correlation with the natural history of the disease in those not on treatment (Lau 1993; Poynard 1997; De Moliner

1998). Patients with a high baseline HCV RNA (considered >2 million copies/mL), faired worse than the patients with low baseline HCV RNA (< 2 million copies/mL). In the combination therapy arms, the virologic SR was 46% for those with low HCV RNA levels compared to 38% for those with high pretreatment viral loads (P < 0.05). The chart below documents the virologic SR rates in genotype 1 patients from the IFN/RBV arms according to baseline HCV RNA:



Approximately 62% and 70% of the patients in the international and U.S. studies, respectively, had baseline HCV RNA > 2 million copies. Likewise, 59% and 72% of patients in the International and U.S. studies, respectively, had genotype 1 HCV. A majority (~2/3) of patients in these studies, had negative prognostic factors and were only able to achieve a 27% virologic SR. Thus, patients considering therapy should be given in understandable language as much information as possible, including 1) virologic status (e.g., HCV RNA level and genotype); 2) histologic status (e.g., stage and grade); 3) results of past studies broken down by good and poor viral and host prognostic factors; 4) known side effects (constitutional, psychological, and hematological); 5) U.S. and European guideline indications for therapy (e.g., "those with progressive disease"); and 6) HCV natural history data (i.e., estimated time to cirrhosis) if untreated. Only then can patients make an informed decision regarding the risks and benefits of starting treatment.

Optimal Course of Therapy: New Guidelines

In both studies, all patients who achieved a virologic SR were HCV RNA-undetectable by week 24. This suggests that if a patient is not undetectable by week 24, he or she never will be, and therapy can be discontinued (Hoofnagle 2000). Interestingly, 14% of the combination therapy patients who had detectable HCV RNA at the 12-week interim analysis went on to achieve an SR (4% and 10% in the 24-week and 48-week arms, respectively) (Poynard 2000). Thus, the old guideline of stopping IFN monotherapy at week 12 (the "3-months rule") if HCV RNA is still detectable, should be replaced by the "6-month stop rule" when combination therapy is used (Hoofnagle 2000).

The NIDDK, in its continual update of the 1997 NIH Consensus Panel's recommendations, has proposed new treatment guidelines for the use of combination IFN/RBV in patients

with chronic HCV (NIDDK 2000). The new guidelines in a treatment algorithm are listed below:

NIDDK's Algorithm for Treatment of Patients with Chronic HCV
Make the diagnosis based on aminotransferase elevations, anti-HCV and HCV RNA in serum, and chronic hepatitis shown by liver biopsy. ~
Assess for suitability of therapy and contraindications. ~
Test for HCV genotype. ~
Discuss side effects and possible outcomes of treatment. ~
Start therapy with alpha interferon 3 million units by subcutaneous injection thrice daily and oral ribavirin 1,000 or 1,200 mg daily. ~
At weeks 1, 2, and 4 and then at intervals of every 4 to 8 weeks thereafter, assess side effects, symptoms, blood counts and aminotransferases. ~
At 24 weeks, assess aminotransferase levels and HCV RNA. In patients with genotypes 2 and 3, stop therapy. In patients with genotype 1, stop therapy if HCV RNA is still positive, but continue therapy for a total of 48 weeks if HCV RNA is negative, retesting for HCV RNA at the end of treatment. ~
After therapy, assess aminotransferases at 2- to 6-month intervals. In responders, repeat HCV RNA testing 6 months after stopping.

(NIDDK 2000)

In a recent publication, Poynard and colleagues contend that in order to minimize relapse, treatment duration of IFN/RBV in naive patients should be based on several prognostic factors rather than simply the patient's genotype (Poynard 2000). In an analysis of the 1,774 patients from the U.S. and international IFN/RBV registrational studies (McHutchinson 1998; Poynard 1998), five independent prognostic factors were associated

with a virological sustained response: genotype 2 or 3; baseline HCV RNA <3.5 million copies/mL; no or portal fibrosis; female gender; and <40 years of age.

After all patients have completed 24 weeks of combination therapy, Poynard and colleagues recommend:

- Discontinue treatment if the patient has detectable HCV RNA
- If HCV RNA is undetectable:
    - Continue treatment for an additional 24 weeks if the patient has <4 four favorable factor.
    - Discontinue treatment is the patient has >4 favorable factors.

While genotype remains the most significant prognostic factor, this study documents that basing a decision of treatment duration on "one factor among the five is an over-simplification that could lead to errors in different populations and subgroups" (Poynard 2000).

Side Effects

IFN and RBV both have their own well-documented toxicities. The table below lists the known side effects of both drugs:

Major and Minor Side Effects of IFN and Ribavirin	
Drug	Side Effects
Interferon (side effects):	Fatigue, malaise, myalgias (nuscle aches), headaches, poor appetite Depression, irritability, anxiety, emotional lability Difficulty concentrating, forgetfulness, sleeplessness Thrombocytopenia, neutropenia Alopecia (hair loss), shortness of breath Nasal congestion, sore throat, cough, rigors (shivering; hot/cold flashes), pruritus (itching), skin rash
Ribavirin (side effects):	Hemolytic anemia (destruction of red blood cells); decrease in hemoglobin of 2-4 g/dl in the first 1-2 weeks; pruritus (itching); skin rash; shortness of breath; fetal loss or fetal abnormalities
Ribavirin (serious side effects):	Bacterial infections; induction of autoantibodies and autoimmune disease; severe depression; psychosis; disorientation; suicide (attempted and actual);

	vision or hearing loss; tinnitus (ringing/buzzing in the ear); seizures; acute renal or heart failure
(PDR 2000)	

Most side effects are mild to moderate and can be managed with counseling, dose reduction, and specific treatments, including G-CSF for neutropenia and epogen for anemia. Because of the risk of fetal abnormalities, it is imperative that women and men use adequate birth control while using ribavirin and for six months afterwards. If men and women cannot practice adequate birth control, ribavirin must not be used!

In the large, multicenter international and U.S. IFN/RBV studies, side effects were more common in the IFN/RBV combination arm than in the IFN monotherapy arm. Dose reduction was required in 13% of patients receiving IFN compared to 17% of those receiving IFN/RBV. Discontinuation of treatment was more common in the 48-week combination therapy arms than in the 48-week IFN monotherapy arms (20% vs. 8%; $P<0.05$) (McHutchinson 1998; Poynard 1998).

The flu-like symptoms (fever, headache, fatigue) are pronounced in patients receiving IFN. Pre-medication with Tylenol, aspirin, or Advil can help somewhat in lessening these side effects. Most importantly, the reports of acute depression and attempted and actual suicides on IFN must be discussed with patients. Psychological monitoring and possibly a 6 to 12 month course of an antidepressant should be considered.

The 1999 EASL Consensus Statement thoroughly lists contraindications for both IFN and RBV (EASL 1999):

Absolute contraindications to IFN:	Present or past psychosis or severe depression; neutropenia and/or thrombocytopenia; organ transplantation (except liver); symptomatic heart disease; decompensated cirrhosis; uncontrolled seizures
Relative contraindications to IFN:	Uncontrolled diabetes; autoimmune disorders, especially thyroiditis
Absolute contraindications to RBV:	End-stage renal failure; anemia; hemoglobinopathies; severe heart disease; pregnancy; no reliable method of contraception

Relative contraindications to RBV:	Uncontrolled arterial hypertension; old age

Treatment of IFN Relapsers and Non-responders
An IFN relapser is different from an IFN non-responder. The former are those who achieved either a virologic (HCV RNA) or a biological response (ALT) at the end of treatment but were unable to sustain the response off therapy for six months. IFN non-responders are those who failed to achieve either a virologic or biochemical response during treatment. Some patients, however, may have had undetectable HCV RNA at certain times while on therapy.

Davis and colleagues conducted a large, international, multicenter trial randomizing 345 IFN biochemically relapsing HCV patients to receive either IFN monotherapy or IFN/RBV for 24 weeks (Davis 1998). Primary endpoints were virologic and histologic, but not biochemical. The results are listed in chart on the next page:

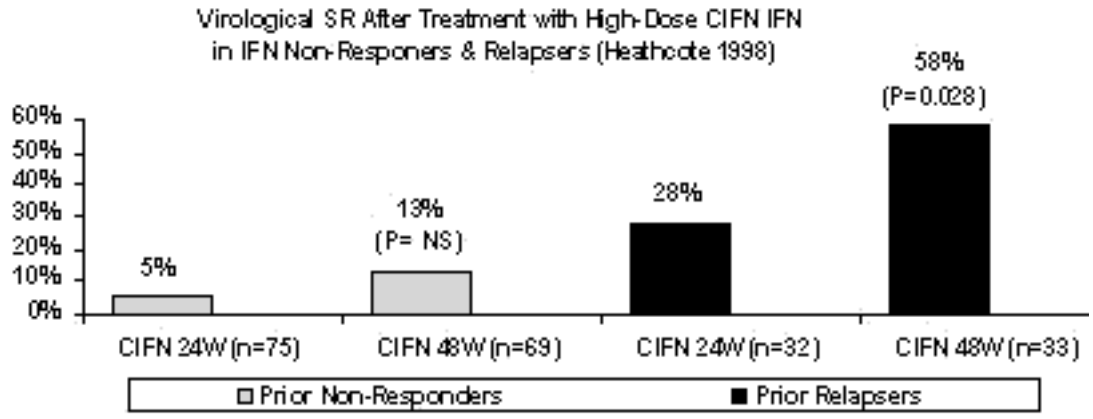
IFN vs. IFN/RBV in IFN Biochemical Relapsers: Treatment Results			
Characteristic	IFN (N = 172)	IFN/RBV (N = 173)	P
Virologic SR	8 (5%)	84 (49%)	<0.001
Biochemical SR	8 (5%)	81 (47%)	<0.001
Virologic + Biochemical SR	8 (5%)	81 (47%)	<0.001
Histologic Improvement	57/138 (41%)	87/139 (63%)	
Genotype			
Genotype 1	3/94 (3%)	29/98 (30%)¥	
Genotype non-1	5/78 (6%)	55/75 (73%)	
Baseline HCV RNA Level			
>2 million copies/mL	2/131 (2%)*	54/128 (42%)**	

<2 million copies/mL	6/41 (15%)	30/45 (67%)
¥ P<0.001 vs. other genotypes. ý P=0.003 vs. HCV RNA <2 million copies/mL Ý P=0.006 vs. HCV RNA <2 million copies/mL		

Obviously, combination therapy is more effective than IFN for retreating IFN relapsers. This study, however, has been questioned for using only 24 weeks of treatment rather than 48 weeks (Hoofnagle 2000). In light of results from the U.S. and international combination therapy studies, it appears that those with genotype non-1 virus will do well with 24 weeks of combination therapy, but those with genotype 1 or high viral loads may be better treated with a 48-week course of therapy.

Follow-up data on the virologic sustained responders from the three registrational IFN/RBV studies (Davis 1998; McHutchinson 1998; Poynard 1998) were presented at the 1999 Annual Meeting of the American Association for the Study of Liver Disease (Davis 1999). Five hundred and fifty-eight of the 2,089 (38.5%) patients in the three studies achieved a virologic SR: 445 to IFN/RBV and 103 to IFN. At the time of analysis, 316 had at least 6 months off-study follow-up. Nine of the 316 (2.8%) had relapsed (became HCV RNA-detectable). While this is a small number of relapsers, and more follow-up time is needed, no significant differences were observed between those who were treatment-naive vs. prior relapser, on IFN vs. IFN/RBV, or with different genotypes or pre-treatment viral loads.

There are little data on the retreatment of IFN non-responders. A study by Heathcote and colleagues took patients who had either relapsed on or never responded to 3 MU of IFN-alfa 2b or 9 micrograms of consensus IFN (CIFN) and randomized them to receive a higher dose of CIFN (15 micrograms) for 24 or 48 weeks (Heathcote 1998). The prior relapsers on the 48 week treatment arm had a significantly higher SR rate than patients in the 24 week arm. There was no significant difference between the two non-responder arms. The virologic SR rates are documented in the chart below:



The response rates documented for prior non-responders may appear low, but they are still improvements over the 1% to 2% response rates seen in other studies where non-responders attempted retreatment with IFN (Marriott 1992; Alberti 1997).

A number of small to medium size IFN/RBV studies have been conducted in IFN non-responders. Cheng and colleagues recently conducted a meta-analysis of 8 randomized controlled trials with a total of 729 patients (Cheng 2000). The overall biochemical and virologic SR rates were 13.3% and 13.7%, respectively.

HCV treatment guidelines are mixed and relatively unhelpful when it comes to advising IFN non-responders. The EASL guidelines, published in 1999, contend, "there are no clear data to indicate that retreatment will be beneficial." The updated NIDDK management guidelines only advises relapsers to consider a 24-week course of combination therapy, but give no guidance to non-responders. They do, however, state the obvious truth: "New medications and approaches to treatment are needed" (NIDDK 2000).

IFN Histologic Improvement in Responders & Non-responders and its Implications

Does histologic improvement prevent the development of hepatocellular carcinoma (HCC; liver cancer) and improve survival? Do patients not achieving a virologic SR on IFN benefit histologically? And, are there any reasons a relapser or non-responder would want to continue on IFN? Nobody knows the exact answers; all three questions remain controversial.

In a retrospective cohort study, Imai and colleagues from Japan studied 563 HCV cirrhotic patients (Imai 1998). All were biopsied, and 419 initiated IFN monotherapy between 1992 and 1993, while 144 served as controls. The endpoint was HCC, and an SR was defined only as a normalization of ALT levels. After a median follow-up of close to four years, 28 (6.7%) and 19 (13.2%) of the IFN-treated patients and controls, respectively, developed HCC (P = 0.04). Only 1 of the 151 IFN patients who achieved an SR developed HCC. The relative risk (RR) for the development of HCC in patients with an SR was 0.06 (95% CI, 0.01-0.46). There was no statistically significant reduction in the relative risk of HCC in the non-responders (RR = 0.51; 95% CI, 0.20-1.27). These data are interesting, and the reduction in HCC in responders appears somewhat promising; however, this was a retrospective cohort study with many limitations. The authors correctly point out two flaws: 1) the wide 95% confidence intervals, stating, "The results suggest that the effect of interferon on the incidence of hepatocellular carcinoma was not very strong;" and 2) insufficient data collection on the use of alcohol.

Fattovich and colleagues from Italy found no statistically significant difference in the development of HCC or in mortality in HCV cirrhotic patients treated with IFN or in controls (Fattovich 1997). In this retrospective cohort study, 329 patients with cirrhosis were followed for a mean period of five years. The yearly incidence of HCC was 2.3% for the untreated controls and 1.0% for the 193 IFN-treated patients. After adjustment for clinical and serologic differences at baseline, the five-year estimated probability of HCC was

2.1% and 2.7% in the IFN and control patients, respectively. There was, however, a reduction in the complications of cirrhosis in the IFN-responding patients.

Shiffman and colleagues followed 53 patients without virologic response to IFN to determine if long-term IFN treatment improved their liver histology (Shiffman 1999). After failing a six-month course of IFN, 27 were randomized to continue IFN for 24 months while 26 went off therapy and were observed. After 30 months of treatment, 80% of 27 patients had histologic improvement with a fibrosis score decline from 2.5 to 1.7 ($P<0.03$). Of the 26 patients who went off therapy, 30% had a worsening of hepatic histology and an increase in mean fibrosis score of 2.2 to 2.4 ($P<0.01$). Interferon does appear to offer histologic improvement even to those who do not respond virologically to IFN. Yet, after two years of being off therapy, less than one-third had a worsening in hepatic histology. Unless we know for certain that improvement in hepatic histology accords real, clinically meaningful benefit (i.e., survival), it is difficult to recommend continued, long-term use of IFN with its pronounced toxicity profile. The decision must ultimately rest with the patient.

HCV Treatment of Selected Patients and Populations

Race as a Prognostic Factor? HCV-infected African Americans and Their Response to IFN

There is a certain amount of controversy about an apparently poorer response to IFN among HCV-infected African Americans than among HCV-infected individuals of other races. In many IFN studies, African Americans have fared poorly on IFN treatment, both as monotherapy and in combination with RBV (Reddy 1999). In the absence of treatment, natural history data suggest that African Americans have less cirrhosis than whites. In a recently presented HCV natural history study of African Americans, Wiley and colleagues documented that after three decades of HCV exposure, 18% of African Americans had cirrhosis compared to 31% of matched non-African-American HCV patients ($P = 0.04$) (Wiley 2000).

Reddy and colleagues, in concert with Amgen's Consensus Interferon (CIFN) Study Group, reviewed results from a 1997 study which randomized 470 patients to receive CIFN (9 micrograms tiw) or IFN alfa-2b (3 MU tiw) (Tong 1997). Specific differences in response rates according to race were analyzed (Reddy 1999). Baseline and treatment results are summarized on the next page:

Baseline, Biochemical, and Virological Results in Four Racial Groups on CIFN

Feature	White Americans	African Americans	Hispanic Americans	Asian Americans	P

N=	380	40	40	10	
Baseline Features					
Sex (male)	74%	63%	70%	10%	NS
Mean ALT (U/L)	132	116	118	117	NS
Cirrhosis	12%	5%	20%	10%	NS
Median HCV RNA	3 million	3.6 million	1.9 million	1.4 million	NS
Genotype 1	66%	88%	69%	40%	0.004+
Biochemical Response					
ETR	44%	13%	25%	40%	0.04+
SR	22%	8%	10%	3%	0.04+
Virologic Response					
ETR	33%	5%	28%	40%	0.04+
SR	12%	2%	10%	30%	0.07+
+ = African American compared to white patients					
(Reddy 1999)					

The median viral load decrease by week 24 on therapy was 2.5 logs in white patients (range: 3.0 to 0.012 million copies/mL) compared to 0.5 logs in the African-American patients (P = 0.014). Nonetheless, for the virologic SR rate -- the primary endpoint of the parent study -- it is important to articulate here that only a non-significant trend was noted in differences between all African-American and all white patients (P = 0.07).

As with other IFN studies, baseline HCV RNA levels (P = 0.0002) and genotype (P = 0.0004) were predictive of a response to therapy. It initially appeared that the higher rate of genotype 1 in African Americans (35 of 40 had genotype 1) was responsible for the difference in response rates. There was a significant difference in EOT response rates in genotype 1 white and African-American patients (22% vs. 6%, respectively; P = 0.038). This difference, however, disappeared in the SR rates (six months after treatment), as 7% in whites compared to 3% in African Americans achieved SR (P = 0.369). When controlling for genotype and HCV RNA in a logistic multiple regression analysis, neither race nor gender was a statistically significant factor associated with a virologic SR. There were also no significant differences in adverse events between races.

Initial differences in HCV treatment response rates between Whites and Blacks were also observed in the two large U.S. and international randomized combination IFN/RBV studies (McHutchinson 1998; Poynard 1998). McHutchinson and colleagues recently presented a retrospective subset analysis of the two studies to determine reasons for differences in response rates between Whites and Blacks3. Only 53 out of the total 1,744 patients were black. The SR rates by race are detailed in the tables below:

Virological SR Rates in Four Racial Groups from the U.S. & International IFN/RBV Randomized Controlled Trials

Treatment Arms	White (N = 1,600)	Black (N = 53)	Hispanic (N = 32)	Asian (N = 27)	P
Combined	434/1,600 (27%)	6/53 (11%)	5/32 (16%)	12/27 (44%)	0.01
IFN/RBV	346/925 (37%)	6/28 (21%)	4/15 (27%)	11/20 (53%)	
IFN	88/675 (13%)	0/25 (0%)	0/12 (0%)	1/7 (14%)	

Baseline Differences between Whites and Blacks

Baseline Features	White	Blacks	P
Genotype 1	65%	96%	<0.0001
Median Age	42 years	45 years	0.0006

Median Weight	79 kg	90 kg	<0.0001
HAI Score	7.1	7.8	0.03

No other baseline differences, such as HCV RNA-level or ALT, were observed. There were no differences in the treatment adherence rate (as measured by pill and vial count) between Whites and Blacks.

After controlling for genotype, there was no difference in the SR rate between Whites and Blacks (P = 0.24). Similar to the findings by Reddy and colleagues, however, there was a significant difference (after controlling for genotype) between the groups in median viral load decreases by week 24 on therapy. According to McHutchinson, "These observations suggest that there may be inherent host differences among racial groups" (McHutchinson 1999).

Results from both studies are intriguing. These results were from post-hoc subset analyses, and the disproportionate number of Blacks/African Americans to Whites (83 vs. 1,980) makes it difficult to draw accurate conclusions. There appears to be something different in the way Blacks/African Americans with HCV, compared to Whites, respond to IFN. The answer cannot be that Blacks/African Americans are ubiquitously unresponsive to the antiviral effects of IFN. We know this because Blacks/African Americans with HBV have been shown to actually have a better response to IFN than Whites with HBV. Lau and colleagues demonstrated this fact in their long-term follow-up of HBV patients treated with IFN monotherapy (Lau 1997). It may be the genetic make-up of the HCV virus in Blacks/African Americans that is responsible for the poor response to IFN. Further prospective randomized studies (and, of course, better HCV therapies) are needed to understand this racial difference. I agree wholeheartedly with K. Rajender Reddy's concluding remarks on this issue:

The clinical finding of a low response rate to alfa interferon among African- American patients further supports the urgent need for better therapies of this disease and stresses the importance of evaluating new therapies in all categories of patients. Hepatitis C is reported to be 2 to 3 times more common among African Americans than among non-Hispanic whites. For that reason, African Americans should make up a sizeable proportion of patients enrolled in trials of antiviral therapy of this disease. (Reddy 1999).

Patients with Acute HCV

Approximately 15% to 20% of individuals with acute HCV will completely recover from infection (MJ Alter 1992; Shakil 1995; Villano 1999). Because of the high rate of chronicity, IFN has been studied to determine if immediate treatment can arrest development of HCV before it becomes chronic. Numerous IFN monotherapy treatment studies in patients with acute HCV infection (mostly from blood transfusions) have been conducted since 1989.

Drawing conclusions from these studies has been difficult for at least four reasons: 1) different doses, administration methods (IV vs. SC), and duration (4, 6, 12, 24 weeks) of IFN were used; 2) only a few studies were randomized and controlled; 3) different response criteria (biochemical and/or virologic) were examined; and 4) small sample size (the average study had ~30 patients) (Esteban 1999).

The most common regimen tested has been 3 MU of IFN for 12 weeks. Poynard and colleagues conducted a meta-analysis and identified four randomized controlled trials that used 3 MU for 12 weeks (Poynard 1996).

The 1997 NIH Consensus Panel did not discuss the treatment of patients with acute HCV infection in much detail. Only two sentences were written:

Data suggest a benefit from interferon treatment with higher clearance of HCV RNA in patients with acute hepatitis C. In light of these findings, interferon treatment of patients with acute hepatitis C could be recommended. (NIH Consensus Panel 1997)

Just mentioning that treatment "could be recommended" gives treating physicians little guidance. We may never fully know the most efficacious way to treat (dose, schedule, duration) these patients. According to Juan Ignacio Esteban,

Available data are, however, too limited to give definite guidelines as to the optimal dose, duration and timing, and given the practical eradication of transfusion-associated hepatitis C, it is unlikely that further large controlled trials will ever be conducted to clarify these issues. (Esteban 1999)

HCV Patients with Persistently Normal ALT Levels

Approximately 25% of chronic HCV patients have persistently normal ALT levels, and most have no symptoms related to liver disease (Marcellin 1999). Neither the 1999 EASL or 1997 NIH Consensus Panel recommends treatment for HCV patients with persistently normal ALT levels outside a clinical trial (EASL 1999; NIH Consensus Panel 1997). It is recommended that they be monitored every four to six months.

While median HCV RNA levels do not differ between chronic HCV patients with normal and abnormal ALT levels, individuals with persistently normal ALT levels more often have a milder degree of histologic abnormalities. In an analysis of 16 published studies totaling 447 patients with persistently normal ALT levels, Marcellin found: 24% with normal liver of non-specific changes; 54% with chronic persistent hepatitis; 21% with chronic active hepatitis; and only 0.8% with cirrhosis (Marcellin 1999).

IFN monotherapy studies in this population have similar methodological limitations as acute HCV treatment trials. In Marcellin's analysis, only one published study included untreated controls and one reported on liver histology. Silverman and colleagues found none of the IFN- treated patients achieved a virologic SR or documented change in liver histology one year after therapy (Silverman 1997). Sangiovanni and colleagues randomized

31 HCV patients with persistently normal ALT levels to receive either IFN (3 MU tiw) for six months or no treatment (Sangiovanni 1998). At the end of treatment, no difference was seen virologically; 15 of 16 IFN-treated patients and 14 of 15 controls, respectively, were still HCV RNA-detectable. ALT levels flared up in ten IFN patients and only one control (62% vs. 7%; P< 0.005). It is because of these ALT flare-ups on IFN and the lack of virologic control that IFN is not recommended for the treatment of HCV patients with persistently normal ALTs. Many combination IFN/RBV studies in this population are ongoing, yet none has been published.

HCV Patients with Cirrhosis

The 1997 NIH Consensus Panel and 1999 EASL Consensus Statement both state that HCV patients with clinically decompensated cirrhosis (those with jaundice, ascites, variceal hemorrhage [bleeding from abnormal blood vessels in the esophagus] or hepatic encephalopathy) should not be treated with standard therapy but should be considered for liver transplantation (NIH Consensus Panel 1997; EASL 1999). For patients with compensated cirrhosis, the NIDDK says that therapy "can be offered," and EASL says that they "may be treated." Neither appears convinced by data (mostly Japanese) indicating that IFN reduces the risk of HCC or improves survival. (See "Experimental Treatments" for a discussion of treatment in cirrhotics.)

Children and the Elderly with HCV

A vast majority of IFN and IFN/RBV studies have excluded individuals with HCV under the age of 18 and over the age of 60; thus, there are scant and incomplete data with which to make recommendations on treating children and the elderly.

Smaller studies employing standard dose IFN in children with HCV have shown that response rates are similar to those seen in adults (Ruiz-Moreno 1992; Balistreri 1995). Neither the NIDDK or EASL makes a firm recommendation to treat or not to treat children except to say that: 1) long-term effects of IFN in children (e.g., growth) are unknown; and 2) if children are treated, it should be with IFN monotherapy because the pediatric dose and safety profile of ribavirin in children has not been established (NIDDK 2000; EASL 1999). Nonetheless, in a New England Journal of Medicine review article, Jay Hoofnagle makes the case that IFN treatment in children with HCV might be beneficial:

In view of the findings that adult patients without cirrhosis had better long-term responses than those with cirrhosis, it seems appropriate to treat children with chronic hepatitis C even if symptoms are absent and histologic features of the liver suggest mild disease, as long as serum aminotransferase concentrations are elevated. (Hoofnagle 1997)

The NIDDK does not recommend treatment for all HCV patients over the age of 60, but suggests they be "managed on an individual basis since the benefit of treatment in these

patients has not been well documented and side effects appear worse in older patients" (NIDDK 2000).

HIV/HCV Coinfected Patients

(For a detailed discussion, see "HIV/HCV Coinfection".)
The 1997 NIH Consensus Panel, NIDDK, and EASL state that HIV/HCV coinfected patients either "should" or "may" be treated as long as they have established control of their HIV infection (NIH Consensus Panel 1997; EASL 1999; NIDDK 2000). The NIDDK correctly points out that in coinfected patients with minimal immunosuppression (>400 CD4 cells/mL), responses to IFN monotherapy are similar in frequency to those HCV patients not infected with HIV (NIDDK 2000). Almost all U.S. and international hepatologists interviewed for this report say that they first have coinfected patients begin potent HIV antiretroviral therapy (an HIV protease inhibitor or a non-nucleoside reverse transcriptase inhibitor plus two nucleoside reverse transcriptase inhibitors) to control their HIV, and subsequently treat them for HCV as they would their HIV-negative patients.

There is, however, incomplete data on coinfected patients treated with IFN. All coinfected patients were excluded from every study discussed in this chapter. Most treatment studies conducted in coinfected patients over the past eight years have been non-randomized pilot/safety trials using different response criteria, IFN doses, and treatment durations. The largest IFN coinfection treatment study published to date enrolled a total of 119 patients (90 HIV-positive patients and 29 HIV-negative controls) (Sorriano 1996).

Only a handful of coinfection studies using IFN/RBV combination therapy have been conducted. They have been small safety studies and mostly presented as conference abstracts. Weisz and colleagues from New York conducted a small, 21-patient coinfection study to determine if combination therapy with IFN and RBV was safe and more effective than IFN monotherapy in HIV-positive individuals with HCV. The results looked promising for those in the combination group; however, it is unclear whether combination therapy was better than IFN alone in this study because patients were unevenly randomized into the two treatment arms. What can be said about the combination of IFN and RBV is that it appears safe in people with HIV who are also on potent antiretroviral therapy. The side effects, such as depression, flu-like symptoms and anemia were no more prominent in the combination therapy group than in the IFN monotherapy group.

Conclusion

Less than 50% of individuals with HCV on treatment today are able to clear their HCV virus. The ability to clear virus on IFN and RBV varies according to genotype and baseline HCV RNA level (viral load): those with low HCV RNA (< 2 million copies/mL) and genotype non-1 have an ~65% chance of a virologic sustained response (SR), while those with high baseline HCV RNA and genotype 1 achieve only an ~27% chance of a virologic SR.

Further research is needed to better understand the clinical significance of a long-term virologic response and its impact on liver disease progression, hepatocellular carcinoma and mortality. For some HCV patients, combination therapy may be a "cure," but for the vast majority, more effective and less toxic therapies are needed.

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Patients who weighed <75 kg were administered 1,000 mg/day and those >75 kg received 1,200 mg/day.

The number of patients with genotypes 4, 5, and 6 were too small to measure separately so they are lumped with genotype 1 patients in this analysis.

The printed abstract uses the term Black (upper-case) to describe African-Americans and others of non-white, Hispanic or Asian race. The term Caucasian is used instead of white. In accordance with the abstract, I will use the term Black (upper-case) and Caucasian.

Experimental Treatments and New Areas of Research for Hepatitis C Virus (HCV) Infection

By Michael Marco

> As has been true in the search for the best therapy for HIV infection, it will be a daunting challenge to develop the most effective and least costly combination therapies for HCV infection.
>
> -- TJ Liang, Combination Therapy for Hepatitis C Infection

Introduction: A Plea for More Effective and Less Toxic Therapies

After approximately ten years of experience with interferon (IFN) monotherapy and two years with combination IFN and ribavirin (RBV), less than 50% of individuals with HCV on treatment today are able to clear their HCV. We have learned that the ability to clear virus on IFN and combination therapy varies according to genotype and baseline HCV RNA (viral load); those with low HCV RNA (<2 million copies/mL) and a non-1 genotype have about a 65% chance of achieving a virologic sustained response (SR), whereas those with high baseline HCV RNA and genotype 1 have only about a 27% chance of similar treatment success (McHutchinson 1998; Poynard 1998). This latter group, with only a 1-in-4 chance of responding to combination therapy, describes the majority of HCV-infected individuals in the U.S. Approximately 75% of HCV-positive individuals have genotype 1 (Alter 1998), and the median HCV RNA viral load observed in recent natural history studies is near 5 million copies/mL (Thomas 2000). Because IFN/RBV-with its myriad constitutional side effects and hematologic toxicities-is certainly not going to benefit a majority of the HCV-positive individuals who need it, new, potent, safe, and effective antiviral agents for the treatment of HCV are badly needed.

The prospects for future treatments for HCV, including targeted HCV antivirals such as protease, helicase, and ribozyme inhibitors, are scientifically rich and exciting. However (and unfortunately), the word "future" must be emphasized because only one of these, a ribozyme inhibitor, has begun clinical trials. Until novel targeted antivirals are available, it is imperative that we improve our standard of care by optimizing the use of our available arsenal.

HCV RNA Viral Kinetics and Optimizing IFN Administration

Current HCV clinical trials continue to search for the optimal way to administer IFN. HCV RNA kinetics data, originally from Neumann and colleagues in 1998, demonstrate that continued and adequate HCV viral suppression is usually not achieved when using 3 MU of IFN three times a week (tiw) (Neumann 1998). HCV production can be as high as 1 x 109 virions (one trillion) per day, and the half-life of HCV is about 2.7 days. When IFN is administered, there is a two-phase decay process. The initial phase gives rise to a rapid decrease and inhibition of HCV RNA production; the second phase involves a slower decay. Viral decay is not always sustained, because the 3-MU dose of IFN appears to block viral

production for only approximately 36-48 hours. The virus is able to rebound and replicate for 24-36 hours until the next IFN dose is administered.

Daily dosing of IFN has been suggested as a way of preventing the rebound of HCV viral production. Numerous clinical trials around the world are looking at both daily and higher initial doses of IFN (so-called induction therapy), either alone or in combination with RBV. Gonzales and colleagues recently presented results of a study comparing a four-week high-dose IFN induction regimen to a standard IFN regimen (Gonzales 2000). In this 48-week study, 135 untreated patients were randomized to receive 5 MU of IFN alfa-2b daily for four weeks followed by 5 MU tiw or 5 MU of IFN alfa-2b tiw. Seventy-six percent of the patients had HCV genotype 1, and 23% had stage 3-4 fibrosis. A virologic SR rate was observed in 14 of 67 (21%) patients in the induction group and 13 of 68(19%) controls (P = NS). Virologic SR rates were higher in the non-1 genotype group, yet no significant differences were noted between the treatment arms in the respective genotype groups. A trend toward more adverse events requiring IFN discontinuation was documented in the induction group compared to the standard group (34% vs. 20%; P = 0.08).

Recently presented results from an Austrian study using IFN induction therapy in combination with RBV did not show an improvement in virologic SR rates over what has previously been reported in the literature (Ferenci 2000). In tests of several induction regimens (5 MU, 10 MU, QD or Q2D) no statistically significant differences were documented among the three arms, which averaged a 37% virologic SR rate.

HCV treatment studies have also tested the strategy of using four-week high-dose IFN induction therapy before adding RBV. Two recently presented studies observed no significant differences in virologic ETR between patients who started with IFN monotherapy induction regimens and those who received standard dosing of IFN/RBV (Cheng 2000; Flamm 2000).

While based on elegant kinetics data, studies reveal that using IFN in higher doses and more often than tiw does not achieve any additional clinical antiviral benefit. Nonetheless, research on HCV viral kinetics -- and the impact of IFN -- is still a new field, and work in this area is considered by many to be crucial for understanding the virus.

Another question yet to be answered is: What is the optimal dose of RBV? Schering has refused to conduct large randomized controlled trials to ascertain if lower doses of RBV -- 600 or 800 mg -- are less toxic than, and as effective as, standard doses. Some researchers contend that Schering has this data (and has even commissioned studies), but will not release the results.

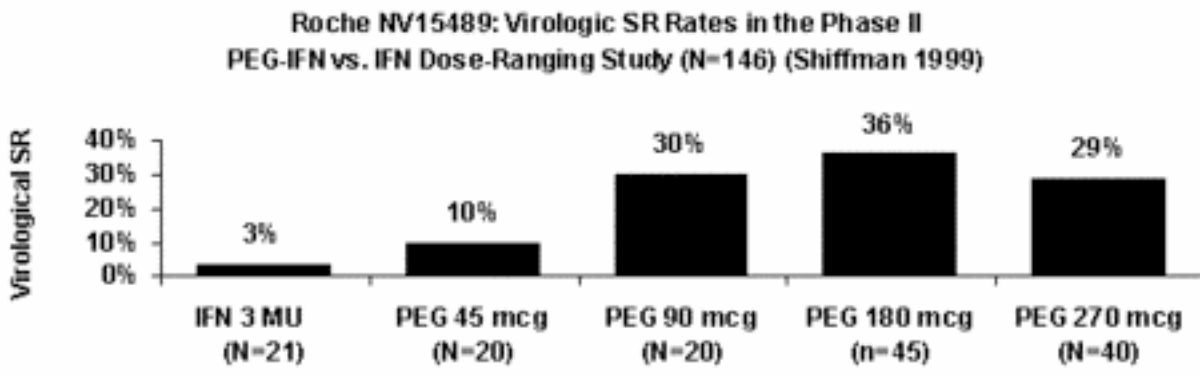
Pegylated Interferons

Pegylated interferons are a formulation of IFN alfa in which IFN has been covalently bonded to polyethylene glycol (PEG). This modification allows for a much longer IFN half-life and a minimized peak-trough ratio. PEG interferons can be administered weekly (instead of tiw with standard IFN) at higher doses that produce improved antiviral activity

due to more consistent circulating levels of IFN. Phase III data have recently been presented, and new drug applications (NDAs) submitted to the FDA for two different PEG interferon formulations: Hoffmann-LaRoche's 40 kDa branched pegylated IFN-a-2a (PEG-IFN; Pegasys?) and Schering Plough's 12 kDa branched pegylated IFN-a-2b (PEG-Intron). Clinical study results have been presented at major hepatology meetings but are not yet published. Data on both PEG interferons document that they are superior to standard IFN. Since they have not been tested head-to-head, it is not yet possible to tell which PEG interferon is more effective.

PEG-IFN (Pegasys™): Hoffmann-LaRoche

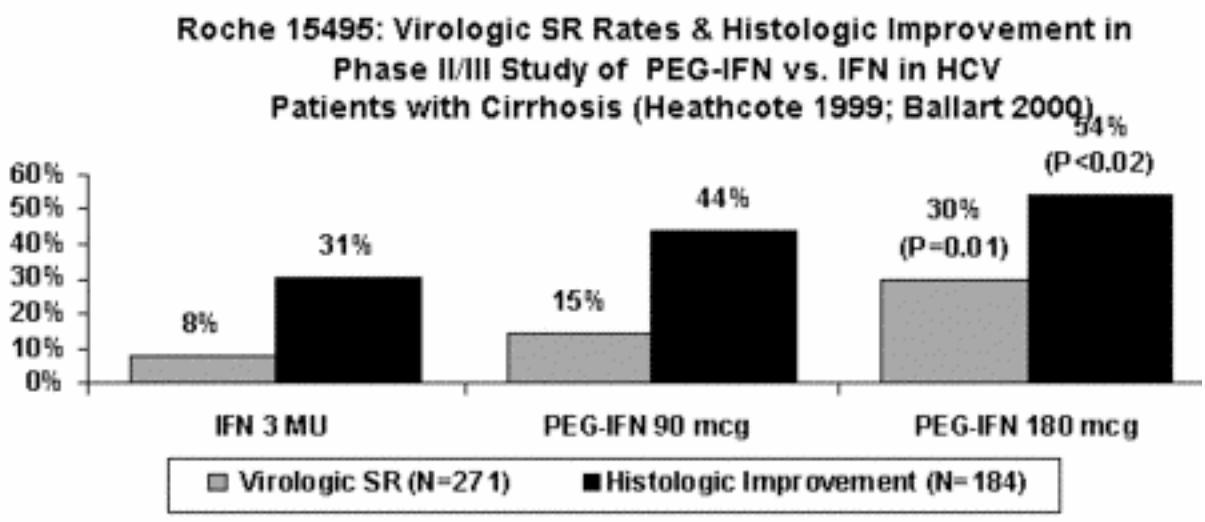
Roche conducted a sound and thorough development plan for its PEG-IFN. Four efficacy studies were conducted totaling ~1,600 patients with ~1,000 receiving PEG-IFN. In Roche NV15489, a phase II dose-ranging study conducted by Shiffman and colleagues, a dose of 180 micrograms (mcg) once weekly was determined to be the most effective (Shiffman 1999). The virologic SR rates are listed below:



The 180 mcg dose was chosen for use in the three registrational PEG-IFN studies. The first of these studies was conducted in HCV patients with cirrhosis. Standard dose IFN monotherapy in cirrhotics has been shown to be relatively ineffective in producing sustained virologic suppression (~10%), and its ability to prevent hepatocellular carcinoma (HCC) and improve survival is debatable (Schalm 1997). In light of these data, U.S. and European HCV treatment guidelines do not universally recommend that cirrhotics receive therapy, yet say they "can" or "may" be treated (NIDDK 2000, EASL 1999). Roche was bold and conducted study NV15495, a 271-patient phase II/III trial comparing two doses of PEG-IFN (90 and 180 mcg) with standard IFN therapy for 48 weeks (Heathcote 1999; Ballart 2000). This is the largest prospective randomized study in cirrhotics ever conducted. The baseline demographics and disease characteristics and study results are listed below:

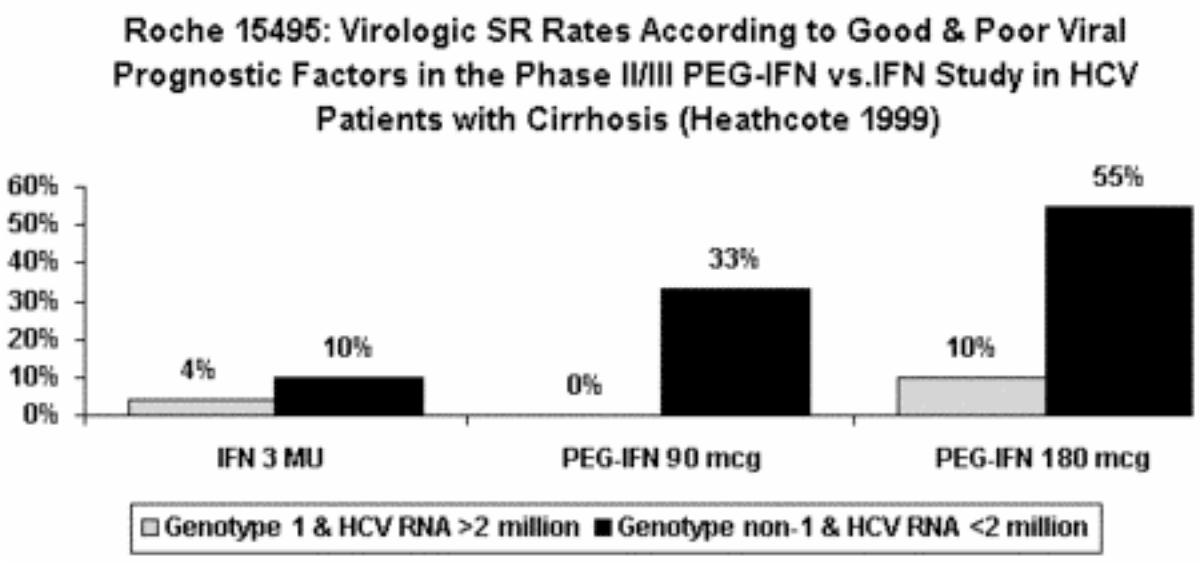
Roche 15495: Phase II/III Study of PEG-IFN vs. IFN in HCV Patients with Cirrhosis:

Baseline Demographics and Disease Characteristics (Heathcote 1999; Ballart 2000)			
	IFN 3 MU (N=80)	PEG-IFN 90 mcg (N=96)	PEG-IFN 180 mcg (N=87)
Gender (male)	70%	74%	72%
Mean Age (years)	47	47	47
Race (White)	88%	91%	86%
Median HCV RNA	3.2 million	2.8 million	2.8 million
Genotype 1	53%	60%	55%
Cirrhosis/transition to cirrhosis cirrhosis	76% / 24%	79% / 21%	79% / 21%



Never before had a prospective, randomized HCV clinical trial in cirrhotics documented a 30% virologic SR or 54% histologic improvement. Likewise, ~34% of PEG-IFN patients who did not achieve a virologic SR had documented histologic improvement. In many patients with cirrhosis, any decrease in histologic activity is needed and welcome. Response rates were not inflated by the 22% of patients with transition to cirrhosis. In fact, in the 180-mcg arm, the cirrhotics achieved a 32% virologic SR compared to 22% in the transition-to-cirrhosis patients.

As impressive as these results appear, there continues to be a marked difference in response rates between those with genotype 1 and non-1. In the 180-mcg arm, the genotype-1 patients achieved a 13% virologic SR compared to 53% in patients with genotype non-1. The response rates, documented in the chart on the next page, are further splayed when analyzed according to good viral prognostic factors (genotype non-1 & HCV RNA <2 million copies/mL) vs. poor viral prognostic factors (genotype 1 & HCV RNA > million):

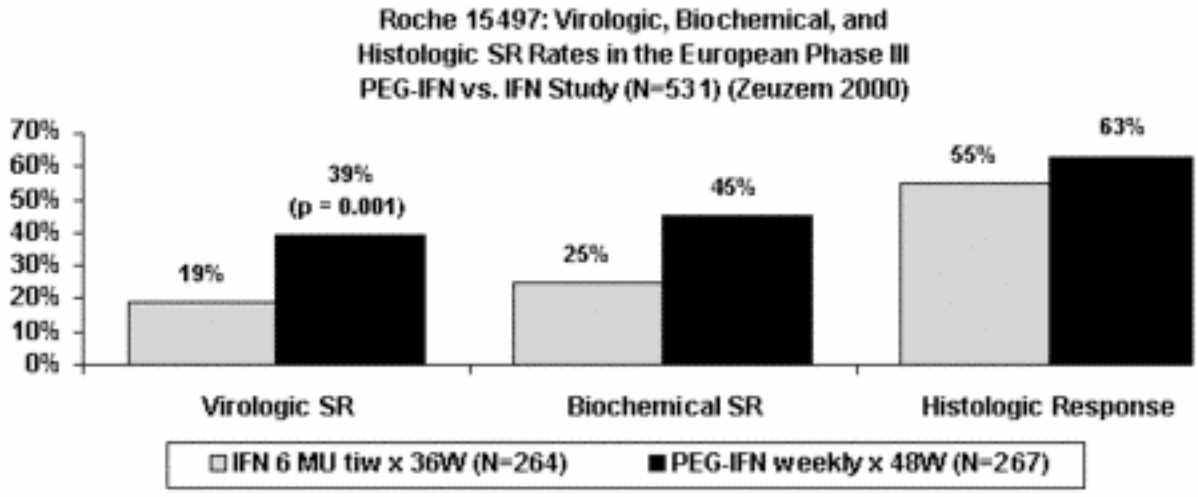


Roche next conducted U.S. and European phase III randomized controlled trials of PEG-IFN vs. IFN. Study NV15497, the 531-patient phase III European trial, was recently presented by Zeuzem and colleagues (Zeuzem 2000). This study compared PEG-IFN 180 mcg weekly vs. 6 MU tiw of IFN. Baseline demographics and disease characteristics, as well as study results, are detailed below:

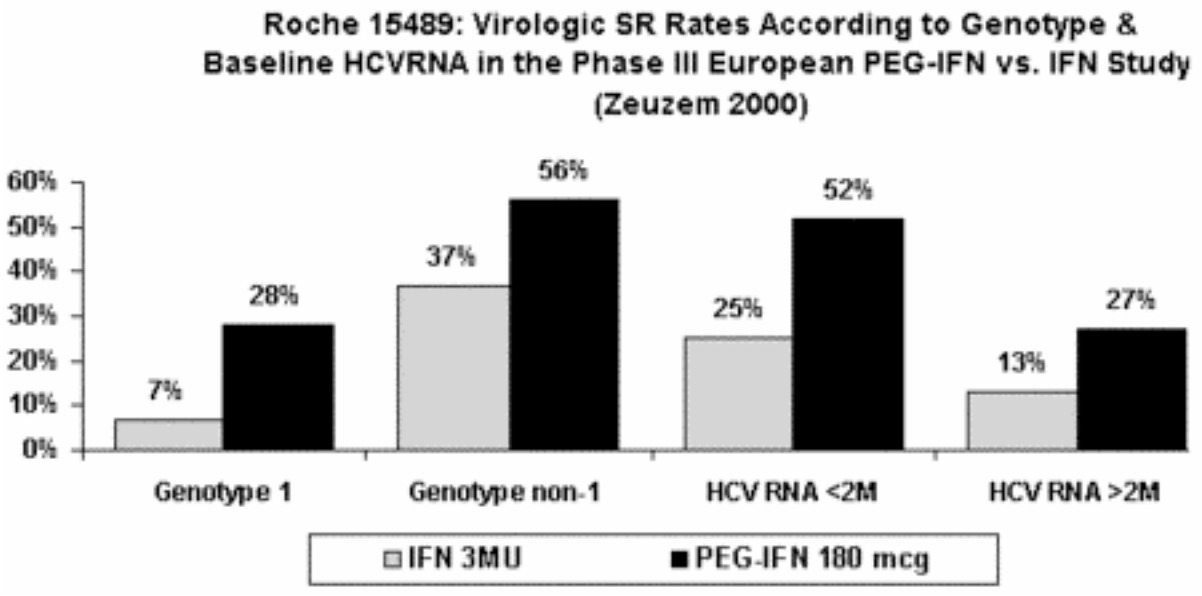
Roche 15497: European Phase III Trial of PEG-IFN vs. IFN in 531 HCV Untreated Patients: Baseline Demographics & Disease Characteristics (Zeuzem 2000)

	IFN 6 MU x 12W & 3 MU x 36W	PEG-IFN 180 mcg x 48W
N =	264	267
Gender (male)	67%	67%
Mean Age (years)	41	40.6

Race (white)	~85%	~85%
Median HCV RNA	8.2 million copies/mL	7.4 million copies/mL
Genotype 1	61%	63%
Mean HAI Score	9	8.6
Cirrhosis or transition to cirrhosis	~14%	~12%



When analyzing the results based on genotype and baseline HCV RNA, the sustained responses are markedly different. The chart below details the 72-week virologic SR rates according to patient's genotype and viral load:



A 28% SR on PEG-IFN is the highest response recorded for genotype-1 patients treated with monotherapy and coincidentally identical to the virologic SR in genotype-1 patients on the IFN/RBV arm of the U.S. phase III IFN/RBV registrational study (McHutchinson 1998).

Roche has not publicly released the results of its U.S. phase III trial (study 15496) and will not until the fall. Study 15496 is a three-arm trial of ~650 untreated HCV patients randomized to receive IFN 3 MU, or PEG-IFN at 135 mcg or 180 mcg. Roche submitted its PEG-IFN NDA to the FDA on 22 May 2000. In a press release Roche contends:

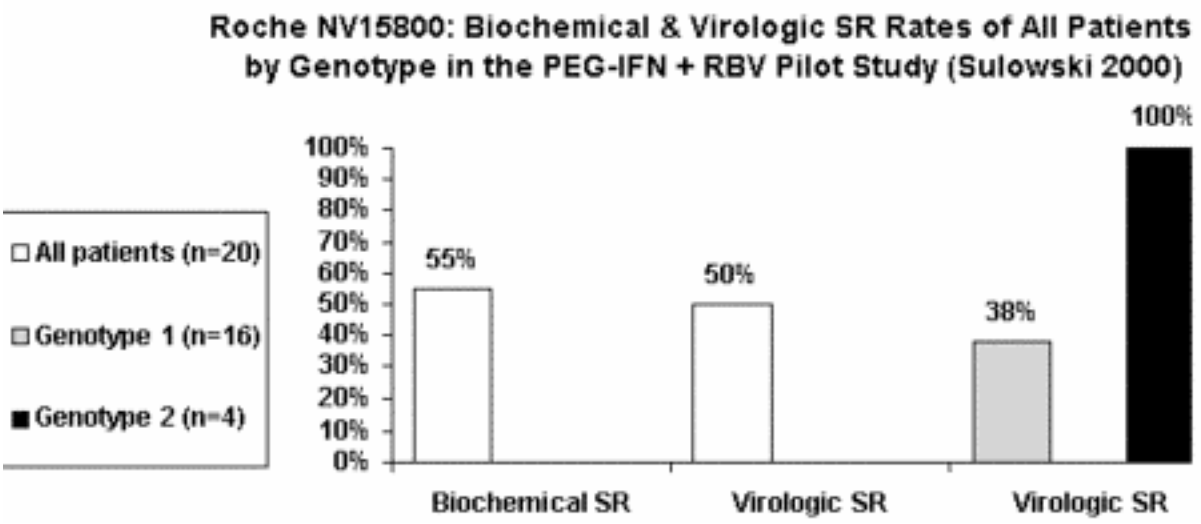
In rigorous intent-to-treat analyses of three pivotal clinical studies involving a total of more than 1,400 patients, those treated with 180 mcg. of PEGASYS had overall sustained virologic responses of 35 percent in patients without cirrhosis and 30 percent in patients with cirrhosis. (Roche Press Release, 5/22/00)

Because the press release reveals a 35% virologic SR in non-cirrhotics, it is obvious they are discussing the results of the 180 mcg arms in the two phase III trials. With a 39% virologic SR in the 180-mcg arm of the European study (15497), the SR in ~215 patients in the 180-mcg arm of the U.S. study must be between 28% and 30% to mathematically achieve an overall 35% virologic SR.

The data from the three studies presented demonstrate that PEG-IFN is significantly more effective than IFN (all P-values were < 0.001). For those in whom ribavirin is contraindicated and cannot initiate combination therapy, PEG-IFN is an excellent alternative and will likely be considered first-line for HCV monotherapy.

When FDA approved, PEG-IFN is expected to be used in combination with RBV. Roche only needs to demonstrate superiority over standard IFN in order for initial FDA approval. In expectation of promising results as combination therapy, and out of the desire to compete

with Schering for its share of the HCV market, Roche is conducting a series of studies testing PEG- IFN with RBV. Sulkowski and colleagues recently presented 24-week follow-up data on a small, 20-patient open-label study of PEG-IFN plus RBV (Sulkowski 2000). Study NV15800 administered 180 mcg of PEG-IFN plus RBV (1,000-1,200 mg) to 16 genotype-1 patients for 48 weeks and to 4 genotype-2 patients for 24 weeks. Study results are listed below:



Safety Profile of PEG-IFN

PEG-IFN appears to have a similar toxicity profile as conventional IFNs. While PEG-IFN offers more convenient dosing and better efficacy, it does not offer fewer or milder side effects. Included on the next page are the integrated safety data from 604 patients receiving PEG-IFN: 323 on IFN 3 MU, and 261 on IFN 6 MU from four studies: NV15489, NV15495, NV15496, and NV15497:

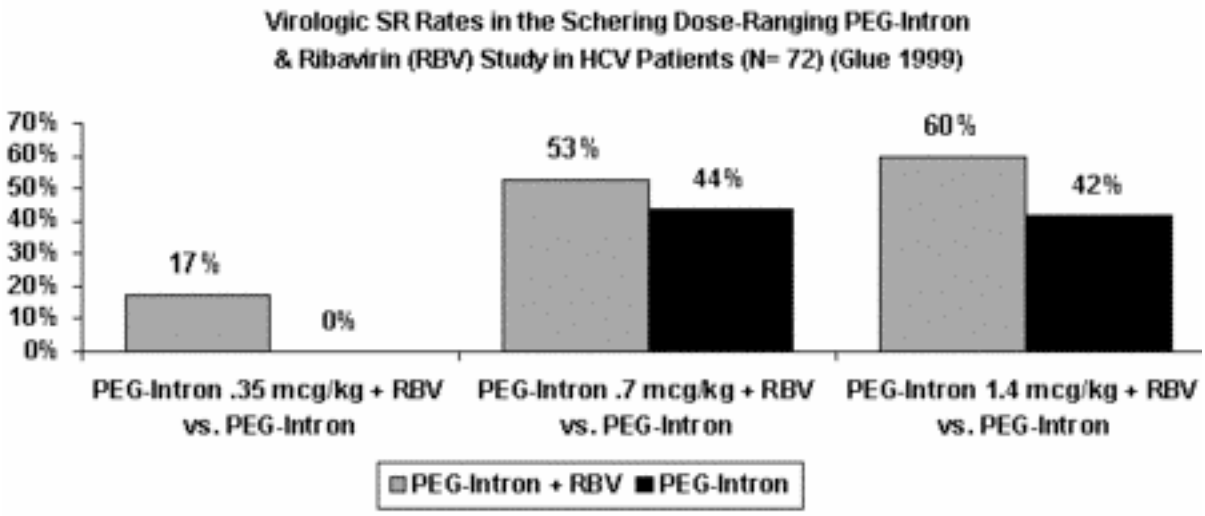
Adverse Reactions Occurring in >10% of Patients in PEG-IFN HCV Trials						
	IFN 3 MU N = 323		IFN 6/3 MU N = 261		PEG-IFN 180 mcg N = 604	
	N	(%)	N	(%)	N	(%)
General						
Fatigue	147	(46)	152	(58)	309	(51)

Rigors	134	(41)	112	(43)	202	(33)
Pyrexia	94	(29)	141	(54)	212	(35)
Injection site reaction	71	(22)	40	(15)	133	(22)
Pain	46	(14)	27	(10)	73	(12)
Gastrointestinal						
Nausea	101	(31)	80	(31)	148	(25)
Diarrhea	44	(14)	48	(18)	103	(17)
Abdominal pain	50	(15)	35	(13)	92	(15)
Nausea and vomiting	19	(6)	25	(10)	33	(5)
Metabolic and Nutritional						
Anorexia	37	(11)	61	(23)	104	(17)
Musculoskeletal, Connective Tissue, and Bone						
Myalgia	115	(36)	108	(41)	218	(36)
Arthralgia	87	(27)	82	(31)	162	(27)
Back pain	31	(10)	27	(10)	51	(8)
Neurological						
Headache	174	(54)	165	(63)	326	(54)
Insomnia	78	(24)	57	(22)	119	(20)
Dizziness (excluding	33	(10)	39	(15)	94	(16)

vertigo)						
Concentration impairment	31	(10)	26	(10)	48	(8)
Psychiatric						
Depression	51	(16)	57	(22)	113	(19)
Irritability	67	(21)	29	(11)	87	(14)
Skin and Subcutaneous Tissue						
Alopecia	78	(24)	92	(35)	141	(23)
Pruritus	20	(6)	24	(9)	68	(11)
IFN = interferon			(Heathcote 1999; Shiffman 1999; Zeuzem 2000; Roche, data on file)			

The genotype-1 patients in the 1.0 and 1.5 mcg/kg PEG-Intron arms achieve only a 14% virologic SR. While it is difficult and unwise to make cross-study comparisons, it is interesting that genotype-1 patients in Roche's European phase III study achieved a 28% virologic SR, exactly twice that achieved in Schering's PEG-Intron trial. The response rate in the 1 mcg/kg arm dropped to 8% for those patients with both genotype 1 and a baseline HCV RNA of >2 million copies/mL.

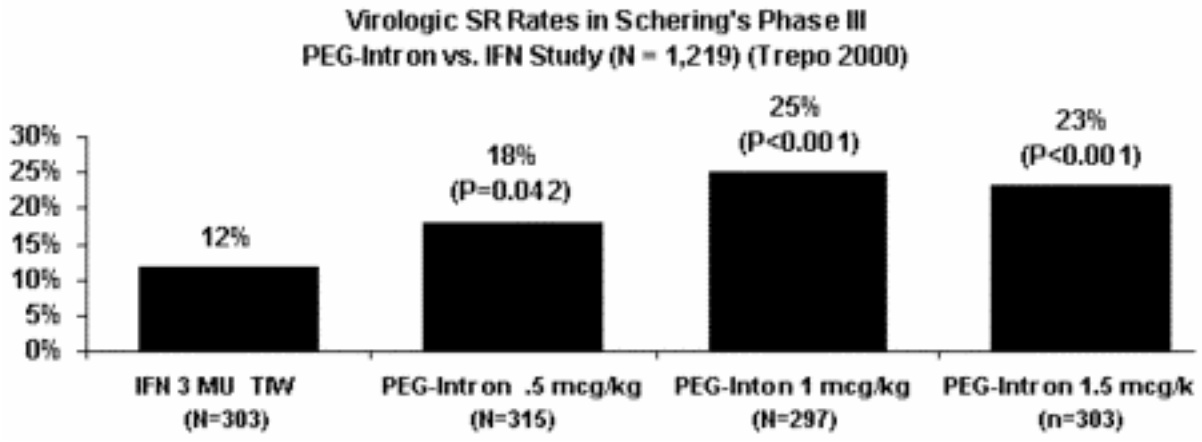
While not a PEG-Intron registrational study, Schering conducted a small-to-medium-sized multi-armed pharmacokinetics (PK), safety, and "efficacy" (Schering's term) study of three doses of PEG-Intron in combination with three doses of RBV compared to PEG-Intron monotherapy (Glue 1999). In this 72-patient study, it appears that patients received at least six different doses of two treatments: PEG-Intron 0.35 mcg/kg, 0.7 mcg/kg, or 1.4 mcg/kg; alone or in combination with RBV 600 mg, 800 mg, or 1,000-1,200 mg. There were 35 men and 37 women ranging from 20 to 68 years of age, and ~50% were infected with genotype 1. PK results demonstrated that "RBV did not alter the PK profile of PEG-Intron," and "PEG-Intron dose-dependently augmented the antiviral activity of RBV." It is difficult to make anything out of the "efficacy" results, and Schering's Paul Glue, during his presentation, said that there was no difference observed in RBV doses, so results were collapsed. The virologic SR rates listed in the chart below are as Schering presented them:



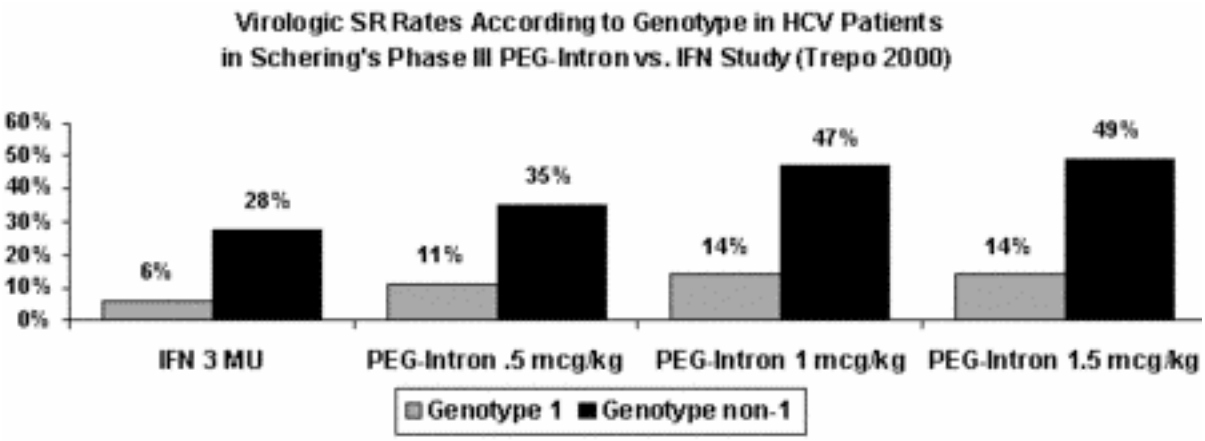
Schering's PEG-Intron development plan was mediocre in demonstrating the efficacy of the 1.0- mcg/kg dose over IFN. The 1.0-mcg/kg dose, which is planned for marketing, was studied in 297 patients and found to be superior to IFN in its only phase II/III dose-ranging study. In contrast, Roche's PEG-IFN 180-mcg dose was used in ~600 patients and found to be superior to IFN in four separate studies. Nonetheless, on 31 May 2000, the European Union granted approval to Schering's PEG-Intron for treatment of patients with HCV. The PEG-Intron NDA was submitted to the FDA on 23 December 2000, approximately five months ahead of Roche's PEG-IFN. It is expected that both will be eventually approved by FDA, which has 12 months to review the applications. Whether the FDA will approve both pegylated interferon NDAs in the order they were received or at the same time (so as to not show favoritism) is anybody's guess. Nonetheless, PEG-IFN has the distinct advantage (at least in the scientific community) of better-documented efficacy and safety data in HCV patients with and without cirrhosis.

Pegylated IFN-a-2b (PEG-Intron): Schering-Plough

Schering's PEG-Intron is a 12 kDa branched pegylated IFN-2a; 28 kDa less than Roche's PEG-IFN. The development plan for PEG-Intron was less rigorous than that for PEG-IFN. Instead of conducting a traditional phase II study to identify the appropriate dose, Schering collapsed the phase and made it part of their registrational phase III study. The study, which randomized 1,219 HCV untreated patients to receive three doses of PEG-Intron or IFN for 48 weeks, was recently presented by Trepo and colleagues (Trepo 2000). There were no significant differences in baseline demographics and disease characteristics among the four arms. The mean age was 43 years; 63% were male; 91% were white; 70% had genotype 1; 74% had an HCV RNA of >2 million copies/mL; and 9% had Metavir grade 3 or 4 fibrosis. Virologic SR rates are documented below:



All PEG-Intron arms were found to be significantly more effective at achieving sustained viral suppression than IFN monotherapy. When stratifying by genotype, SR rates decreased by ~40% in genotype-1 patients and doubled for those with non-1. Likewise, the patients with high baseline viral loads (HCV RNA >2 million copies/mL) did significantly worse than those with low viral loads. The chart below documents the virologic SR rates for all arms according to genotype. PEG-Intron 1 mcg/kg is the dose Schering has submitted in its NDA to the FDA.



The NIH's NIDDK recently gave a thumbs-up to Roche when it chose PEG-IFN as the pegylated interferon it will use in the randomized monotherapy phase of its HALT-C trial. The HALT-C trial (Hepatitis C Antiviral Long-term Treatment against Cirrhosis) is a planned eight-year, 28-million-dollar study of 1,350 IFN or IFN/RBV relapsers with stage 3 fibrosis. At nine selected sites, all will be retreated with IFN/RBV for five months. Those patients not achieving a virologic response will be randomized to receive PEG-Intron or no treatment for another ~3 years to determine if continuing antiviral therapy will decrease the incidence of HCC and increase survival.

Interleukins: IL-2, IL-10, and IL-12

Interleukins are cytokines which are responsible for cell-to-cell communication, inflammatory response amplification, and immune response regulation. Cytokines can be produced by multiple cells in the body, including CD4 and CD8 T cells, and macrophages in response to exogenous and endogenous antigens and bacterial products (Peters 1996). Cytokines are polarized, depending on their phenotype, into type 1 and type 2 helper T cells (TH1 and TH2) (Swain 1990; Mosmann 1991). TH1 cells produce IL-2, IFN-gamma, and tumor necrosis factor (TNF) while TH2 cells produce IL-4, IL-6, and IL-10. Individuals who naturally recover from acute HCV infection have been found to have a strong TH1 response (Diepolder 1995); however, progressive liver disease in chronic HCV has been correlated with an increased intrahepatic expression of TH1 cytokines (Napoli 1996).

Recombinant IL-2 has been studied in patients with chronic HBV and HCV in the hope that IL-2 can shift T-cell responses towards a predominantly TH1-like phenotype and thus facilitate clearing of virus without being necroinflammatory. In a 1993 pilot study, recombinant IL-2 (rIL- 2) demonstrated immunomodulatory and antiviral activity in HBV patients (Tilg 1993). RIL-2 was tested a few years later by Pardo and colleagues in 33 IFN-naive HCV patients (Pardo 1997). The 33 patients were randomized to receive three different doses of IL-2 (0.9, 1.8, and 3.6 MU) five times a week for 12 weeks. At 12 weeks, those who responded stopped treatment while non-responders continued with a higher dose of 5.4 MU. Approximately 24% of patients had normalization of their ALT levels at the end of treatment, yet only 8% had an SR on follow-up. No patient's HCV RNA became undetectable, and no histologic improvement was found. Some 24% to 73% of the patients experienced side effects, including flu-like symptoms, nausea, anorexia and local site irritation.

In mice induced with carbon tetrachloride, IL-10 has been shown to control neutrophilic infiltration, hepatocyte proliferation, and liver fibrosis (Louis 1998). Recombinant human (rHu) IL-10 has demonstrated some activity in HCV patients in two pilot studies. McHutchinson and colleagues conducted a 16-patient pilot study to assess the safety of IL-10 and its ability to normalize ALTs (McHutchinson 1999). Three IFN-naive patients and 13 non-responders received 4 or 8 mcg/kg of IL-10 subcutaneously daily for 28 days. With both IL-10 doses, ALT levels normalized in eight patients at the end of treatment, but returned to pretreatment levels in patients during the four-week follow-up period. There were neither significant increases nor decreases in HCV RNA levels. The only adverse event noted was a transient fall in platelet counts (73,000-63,000) in two patients.

Nelson and colleagues randomized IFN non-responders to receive 4 or 8 mcg/kg of IL-10 for 90 days (Nelson 2000). Nineteen of the 22 patients who completed therapy had a normalization of their ALT levels, yet only four remained normal on follow-up. Hepatic inflamation decreased (>2 decrease in HAI score) in 11 of 22 patients and Ishak fibrosis score decreased in 14 (mean change = 3.6-3.2; P = 0.001). Mild anemia occurred during the first four weeks of therapy in most patients with an average decrease in hemoglobin level of 2.2 g/dl. Side effects, including headache (75%), dry mouth (25%), and insomnia (17%) were more common in the 8 mcg/kg arm.

IL-12, which drives TH1 responses, has shown minimal antiviral activity in patients with HCV. It is not considered to have a promising future for treating HCV. IL-12 was originally

studied for its demonstrated ability to mount an effective cellular response directed towards intracellular pathogens (Scott 1993). In a multinational, Roche-sponsored phase I/II study, Zeuzem and colleagues randomized 60 HCV patients to receive four doses of IL-12 for ten consecutive weeks: 16, 14, 15, and 15 patients at .03, 0.1, 0.25, and 0.5 mcg/kg, respectively (Zeuzem 1999). Mean age was 41 years; 42 patients were male; 24 had previously received IFN; 39 had genotype 1; and median HCV RNA was 480,000 copies/mL.

No patients achieved a virologic end of treatment response, but 20 of the 60 patients did have a >50% decrease in their baseline HCV RNA: 3, 3, 6, and 8 patients on the .03, 0.1, 0.25, and 0.5 mcg/kg doses, respectively. At the end of follow-up, only 5 of 60 patients had a normalization of their ALT levels and significant anti-rHuIL-12 antibody titers were not detectable in any patients. The most common adverse events on IL-12 were: headache (67%); fatigue (32%); rhinitis (28%); fever (28%); and chills (12%). The most frequent laboratory abnormalities were transient decreases in leukocytes in (31 patients; grade I and II) and transient increases in ALT levels (32 patients) and bilirubin (7 patients), most of which returned to baseline.

Because of their limited activity and side-effect profile, cytokines as monotherapy do not appear to be promising for HCV. As adjuvants to HCV antivirals, cytokines may prove to be beneficial. More research will need to be done in this area.

Amantadine (Symmetrel®; Endo) & Rimantadine (Flumadine®; Forest)

Amantadine and its analog, rimantadine, are antiviral agents FDA-approved for the treatment and prophylaxis of influenza A virus. Amantadine is also indicated for the treatment of idiopathic Parkinson's disease and drug-induced extrapyramidal reactions (PDR 2000). Both drugs appear to block the viral membrane matrix protein M2, which plays a central role in virus replication and assembly (Duff 1992). In a recently published in vitro study, amantadine and rimantadine were shown to have no direct inhibitory effects against HCV viral protease, helicase, ATPase, polymerase, and internal ribosomal entry site-mediated translation (Jubin 2000).

In a 1997 pilot study, amantadine monotherapy demonstrated improvement in biochemical and virologic markers for some patient with HCV (Smith 1997). Two later clinical studies of amantadine monotherapy failed to support HCV antiviral effects shown previously (Lynch 1998; Senturk 1998). Results have been mixed in amantadine combination therapy studies. Khalili and colleagues randomized 29 IFN non-responders to receive IFN/RBV (N = 14) or IFN plus amantadine for 24 weeks (Khalili 2000). At the end of follow-up, 2 of 13 (15%) patients on IFN/RBV compared to none of the IFN plus amantadine patients achieved a virologic and biochemical SR. In an Italian triple-combination therapy study, Brillanti and colleagues randomized 20 IFN non-responders to receive IFN/RBV or IFN/RBV plus amantadine for 24 weeks (Brillanti 1999). At the end of the 24 week follow-up period, one of the dual therapy patients had a biochemical SR compared to four triple-therapy patients. Virological SR was achieved in none of the dual-therapy patients and in three on triple therapy.

Amantadine is not without its side effects. Two of 22 (9%) had to discontinue therapy due to cardiovascular adverse events in the original monotherapy study. In other HCV amantadine studies, cardiovascular side effects were only 0.1% to 1% (Younossi 1999). Central nervous system and psychiatric side effects (headache, depression, psychosis, and convulsions) have averaged <5%. Other side effects observed include nausea, vomiting, and diarrhea (5-10%).

Rimantadine monotherapy has proven poor as a treatment for HCV. In two recently published pilot studies (one in IFN non-responders, the other in liver-transplant recipients), no patients achieved a biochemical or virologic response (Fong 1999; Sherman 1999).

It is apparent that neither amantadine nor rimantadine is effective as monotherapy. Because the studies have been so small, there is little that can be said about amantadine's effectiveness in combination therapy regimens. Nevertheless, amantadine in combination with IFN/RBV warrants further investigation in larger studies of untreated and pretreated HCV patients.

Agents in Preclinical and Early-stage Clinical Development

IMPDH Inhibitor: VX-497 (Vertex)

Inosine monophosphate dehydrogenase (IMPDH) is a cellular enzyme that is essential for production of guanine nucleotides, the building blocks of RNA and DNA. Inhibiting IMPDH and thus stopping nucleotide synthesis may be effective in blocking the growth of lymphocytes and virus replication. Ribavirin (RBV) is an IMPDH inhibitor and FDA-approved for the treatment of respiratory syncytial virus infection (in an aerosol) and orally in combination with IFN for treating HCV (PDR 2000). In early HCV studies, RBV monotherapy was shown to decrease ALT levels, yet it had no HCV antiviral activity (Bodenheimer 1997). While it has a synergistic effect with IFN, its exact mechanism of action remains incompletely understood.

VX-497, a new oral antiviral, is a potent IMPDH inhibitor. In vitro studies suggest that VX-497 has increased synergy with IFN and greater activity than that of RBV against DNA and RNA viruses, including HBV, respiratory syncytial virus, and bovine diarrhea virus (Markland 1999). A phase II randomized double-blind placebo-controlled study investigating the PK, safety and antiviral activity of VX-497 was recently presented by Wright and colleagues (Wright 1999). Thirty IFN non-responders were randomized to receive VX-497 at doses of 100, 200, or 400 mg every eight hours or placebo for 28 days. The 200- and 400-mg doses, but not the 100-mg dose, had a mean reduction in ALT levels of 25% and 21%, respectively, compared to placebo (P = 0.01 & 0.04). No significant change in HCV RNA was observed. Studies of VX-497 in combination with IFN are currently being conducted.

Hammerhead Ribozymes: LY466700 (Ribozyme Pharmaceuticals & Eli Lilly)

Ribozymes (ribonucleic acid enzymes) are catalytic RNA molecules that are synthetically engineered to act as molecular scissors capable of cleaving specific RNA sequences.

Hammerhead ribozymes contain a conserved catalytic site flanked by engineered antisense sequences which mediate site-specific binding to the target RNA. By cleaving a highly conserved region of the HCV gene (cutting the HCV), the virus is unable to produce more virus, then dies.

Ribozyme Pharmaceuticals, under the direction of Lawrence Blatt (the wunderkind who shepherded Amgen's Infergen through its FDA approval) has developed LY 466700, a nuclease resistant hammerhead ribozyme targeting the 5' untranslated region (UTR) of the HCV genome at site 195. In female C57/B16 mice, the labeled ribozyme is retained in hepatocytes and endothelial cells lining the sinusoid (Lee 1999). It has been shown to inhibit (>90%) replication of a HCV 5' UTR-poliovirus chimera in cell culture (Macejak 2000). A single-dose safety study of LY 466700 was just completed in healthy normals, and additional clinical studies, including PK, safety, and combination therapy trials with IFN are being planned.

Histamine Dihydrochloride (Maxamine, Maxim Pharmaceutical)
Histamine dihydrochloride (Maxamine) is an experimental agent that inhibits phagocyte-derived oxidative stress and inflamation. It is used as an adjunct to cytokine therapy, namely IL-2, as an experimental treatment for metastatic malignant melanoma and acute myelogenous leukemia (AML). Maxamine in combination with IL-2 was found to be more effective than IL-2 alone in a recent phase III malignant melanoma study. In February 2000, the FDA granted Maxim Pharmaceuticals orphan drug status for Maxamine as an adjunct to cytokine therapy for the treatment of metastatic malignant melanoma. An NDA for Maxamine as an adjunct to IL-2 will be filed in the summer of 2000.

Maxamine in combination with IFN is also being studied in HCV patients. A 12-week interim analysis of a phase II dose-ranging study of Maxamine plus IFN was recently presented by Lurie and colleagues (Lurie 2000). One hundred twenty-nine IFN-naive patients were randomized to receive 3, 5, 6, or 10 mg subcutaneously daily plus 3 MU of IFN tiw. All patients received 12 weeks of therapy, and those responding will continue treatment for an additional 36 weeks. Mean age of patients was 30 years; mean HCV RNA level was 6.7 million copies/mL, and 47% had genotype 1. After 12 weeks on therapy, 53-83% of all patients became undetectable (< 1,000 copies of RNA). In those with genotype 1 and high viral loads, 48 - 77% achieved a virologic response. Side effects included flushing, headache, hypotension, and increased heart rate. Not much can be said about Maxamine until the 72-week data are analyzed. Nonetheless, the company is already planning studies of Maxamine in combination with IFN/RBV.

Antisense Oglionucleotides
Antisense oglionucleotides are designed to bind to specific sequences in the viral RNA, resulting in RNA-RNA hybrids that stop RNA replication, reverse transcription, or mRNA translation (Davis 1999). A number of recent in vitro studies have shown that specific antisense oglionucleotides can successfully inhibit translation of HCV RNA (Alt 1999; Brown-Driver 1999; Wakita 1999). All are in preclinical development. Hepatologist Gary Davis urges caution about the use of antisense oglionucleotides in humans. He writes:

The major drawbacks of antisense oglionucleotides relate to the potential for non-antisense effects, such as destruction of untargetted cellular mRNA, and inappropriate activation of cellular enzymes (2'5' oligoadenylated sythetase, protein kinases, endonuclease RNase L) and upregulation of interferon production of double-stranded RNA in uninfected cells. (Davis 1999)

Inhibition of Viral Replication by Enzyme Inhibition: HCV Protease & Helicase Inhibitors
In 1996, the three-dimensional X-ray crystal structure of the HCV NS3 protease domain was solved by Kim and colleagues from Vertex Pharmaceuticals and Love and colleagues from Agouron Pharmaceuticals (Kim 1996; Love 1996). This was exciting news, and there were high hopes for a potent HCV protease inhibitor that would do for people with HCV what HIV protease inhibitors had for people with HIV/AIDS. Four years later, no company has yet identified a compound that is nearing studies in humans. Many companies, including Schering, Gilead, Roche, Glaxo Wellcome, Merck, Boehringer Ingelheim, and Chiron are believed to be working on identifying an HCV serine protease and/or helicase inhibitor. There are at least three major reasons why research development in this area has been so slow: 1) the lack of reliable and efficient cell culture systems; 2) the lack of a small-animal model (the only animal model is the chimpanzee); and 3) heinous lawsuits from Chiron over patent infringement of HCV technology. According to John Cohen from Science,

The lawsuits involving HCV drug R&D center on efforts to find drugs that block the viral protease enzyme, on which Chiron holds patents. The company [Chiron], arguing that its competitors need this enzyme to screen for compounds that inhibit it, filed suit against Agouron, Gilead, and collaborators Vertex and Eli Lilly to try to force them to pay licensing fees and then royalties if one of their protease inhibitors goes to market. (Cohen 1999)

These patent lawsuits also cover development of an HCV helicase inhibitor. The three-dimensional X-ray crystal structure of the HCV helicase was first solved by Yao and colleagues from Schering in 1997 and later by Kim and colleagues from Vertex in 1998 (Yao 1997; Kim 1998). The lawsuits have not prevented researchers from screening numerous compounds. No one will speak publicly about their development plans for protease or helicase inhibitors or even mention particulars about the lawsuits. One high-profile chemist I recently spoke with was reticent to give me much pertinent information on his company's protease inhibitor drug discovery effort, but when asked if he was bothered that the lawyers were making more money than he was, he laughed and said, "Yes."

Progress on the vaccine front is also very slow. The EASL Guidelines committee sadly concludes that "A traditional vaccine is unlikely to become available in the foreseeable future" (EASL 1999). Vaccine research is hampered by the same three reasons mentioned above, as well as by the high mutability of the HCV viral envelope proteins (E1/E2).

Conclusion

There is great need for new, potent, effective, and safe HCV antiviral drugs which can stop or delay progression to liver disease. Until they arrive, we will have to prepare for the new pegylated interferons and wait to see how well patients -- in all populations -- respond to

them in combination with ribavirin. Unless the majority of patients with HCV (those with genotype 1 and an HCV RNA >2 million copies/mL) have better than a 50% chance of clearing their virus, U.S. and international HCV treatment guidelines must still be followed: "Therapy for chronic hepatitis C is indicated for patients who have persistently abnormal ALT (greater than six months), a positive HCV RNA, and a liver biopsy demonstrating either portal or bridging fibrosis and at least moderate degree of inflamation and necrosis" (NIH Consensus Panel 1997).

The NIH and subsequent NIDDK guideline are fortunately devoid of pharmaceutical company oversight and approval. Cost-benefit analyses, and data funded by Schering which say that current treatments are beneficial for HCV patients with "mild" histologic disease, appear to be more marketing ploys than hard science (Wong 1998; Fang 1999). According to Robert Levine, rationally sound advice is warranted:

I will continue to advise a tincture in time for most of my patients with histologically mild chronic hepatitis C, both because I do not believe that their prognosis is as daunting as is often stated and because the outlook for new and more effective therapies is promising. (Levine 1998)

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Note: The 6-MU tiw dose of IFN is double the standard dose of 3 MU tiw. Roche's Roeferon is approved in the U.S. at the 3-MU dose; the 6-MU dose is indicated only for re-treating IFN-relapsers (PDR 2000). In Europe, however, the 6 MU dose is indicated for the first three months, followed by the 3-MU dose.

Hepatitis and HIV Coinfection

By Jeffrey Schouten

Epidemiology

The parallel epidemics of HCV and HIV infection became inextricably intertwined as the incidence of intravenous drug use (IVDU) increased in the population of people infected with HIV. It is estimated that up to 240,000 people are now coinfected with HCV and HIV in the U.S. (Sulkowski 2000b). While the prevalance of HCV infection among injection drug users (IDUs) is much higher than that of HIV infection, alarming increases in the number of people coinfected with HCV and HIV continue to be reported. Studies of various populations worldwide report coinfection in 23% to 75% of IDUs (Dieterich 1999a; Matthews 2000; Sulkowski 2000b). A study of 213 HIV-positive people -- of whom 35% were coinfected -- determined that people between ages 40 and 49 had the greatest risk of being found HCV-infected. No correlation was found with gender or race (Sherman 2000).

The presence of HIV infection can diminish the accuracy HCV antibody assays. There is an increased risk of receiving both false-negative and false-positive results from HCV screening antibody tests in people with HIV infection (Zylberberg 1996b; George 2000). The current USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus recommend that positive screening antibody tests for HCV in people with HIV should be confirmed with either the recombinant immunoblot assay (RIBA) or an HCV RNA test. In addition, it is recommended that HIV-positive people with undetectable HCV antibodies, but evidence of unexplained chronic liver disease, should have an HCV RNA test performed (CDC 1999).

Natural History of HCV/HIV Coinfection

Almost all studies of people coinfected with HCV and HIV have reported that while the progression of HIV disease is not strongly influenced by HCV infection, hepatitis C progresses more rapidly in people with coinfection (Wright 1994; Sánchez-Quijano 1995; Zylberberg 1996b; Soto 1997; Piroth 1998; Staples 1999). Most of the above studies show that people with HCV/HIV coinfection experience a faster progression to cirrhosis, and have evidence of more extensive liver damage (Garciá-Samaniego 1997). Staples compared time from HIV diagnosis to AIDS, time from diagnosis of HIV to death, and time from diagnosis of AIDS to death in 350 people, of whom 33% were HCV/HIV coinfected, and found that HCV coinfection did not adversely impact any of those measurements (Staples 1999). A study of 111 HCV/HIV hemophiliacs, infected between 1979 and 1985, reported that people infected with HCV genotype 1 experienced a more rapid progression to AIDS and AIDS-related death (Sabin 1997).

When matched for other variables, on average, people who are HIV-positive have higher levels of HCV RNA than HIV-negative people (Eyster 1993, 1994; Cribier 1995; Thomas 1996; Beld 1998; Bonacini 1999). However, Cribier did not find a correlation between HCV

RNA and either CD4 count or HIV RNA copy number, suggesting that there is no "direct interaction between HCV and HIV."

Relationship between HCV RNA and HIV Stage							
HIV Stage	A1	A2	A3	B2	B3	C2	C3
Number	3	19	7	10	26	1	9
% HCV RNA+	67	84	100	90	96	0	100
Mean HCV RNA (X10 5)	149.5	174.6	196.9	120.5	125.5	-	83.8
(Cribier 1995)							

Relationship between Serum and Hepatic HCV RNA and HCV/HIV			
	HCV	HCV/HIV	P-value
Serum HCV RNA (log copies/mL)	6.2	6.7	0.02
Liver HCV RNA (log copies/ìg)	2.19	2.90	0.04
(Bonacini 1999)			

Some researchers recommend that HCV be thought of as an opportunistic infection in people with HIV because of a more rapid progression to death due to liver disease associated with HIV coinfection. Although, they note that it remains to be seen if highly active antiretroviral therapy (HAART) and suppression of HIV RNA will lower the incidence of progressive liver disease in people with HCV/HIV coinfection (Lessens 1999; Sulkowski 2000b). The following factors were shown to be associated with the higher liver fibrosis progression rate observed in HCV/HIV coinfected people: low CD4 count, higher alcohol consumption, and age at HCV infection (>25 years old) (Benhamou 1999b).

Two major limitations exist, however, in the above data. First, the sequence of acquisition of HCV and HIV may affect the prognosis of each. HCV is much easier to transmit through parenteral exposure than is HIV, such as when sharing needles. Thus, it is possible that

many people first become infected with HCV, and then, at a later date, become HIV-infected. One report showed that when a person acquired HCV and HIV simultaneously, it took much longer than normal for that person to develop antibodies to both HIV (8-9 months) and HCV (9-13 months). This person, a healthcare worker, had rapid progression to hepatic failure and death (Ridzon 1997); however, a subsequent report detailed another person who was simultaneously infected with HIV and HCV, who had developed antibodies to both at the expected time (one month for HIV, and four months for HCV), who was symptom-free four years later (Biron 1997). Most studies of HCV/HIV coinfected people, however, do not report data based on the sequence of acquisition.

Second, the majority of the data about prognosis are from the pre-HAART era. There is a suggestion that HAART may alter the rapid progression of HCV, so that HCV disease progression may be closer to that observed in HIV-negative people when people are on HAART (Benhamou 1999a). Tor studied liver biopsies in 162 HCV/HIV coinfected people on HAART who had stabilized HIV disease and did not find any differences in liver inflammation and fibrosis, compared to age-matched HIV-negative, HCV-infected people (Tor 2000). Thus as the immune system recovers on HAART, people with HIV infection may be able to "control" HCV, or at least live a longer time, before developing clinically significant liver damage. Much more research is acutely needed in this area; however, as discussed in the "HCV pathogenesis" section of this report, our understanding of mechanisms of immunologic response, liver damage, and potential control of HCV is very limited at this time.

The few studies which suggest that HCV progression is slowed in people on HAART, or protease inhibitors, have very serious limitations (see "Treatment of Hepatitis C Virus"). There is a great deal of patient selection when comparing a group of people who are on HAART to people not on HAART in any retrospective, non-randomized study. Active substance use, poor compliance, HIV RNA (viral load), CD4 (T helper) cell counts, coexistent mental illness, insurance, socioeconomic status, and other factors may contribute to the worse prognosis of HCV. None of the currently available studies provide enough comparative data to assess the comparability of these factors in the people treated with HAART compared to the people not treated with HAART. There is an urgent need for studies to address this critical issue, as it has a direct bearing on how aggressively HIV should be treated in HCV/HIV coinfected people.

It is also unknown whether people with HIV more easily acquire HCV, and conversely, whether people with HCV more easily acquire HIV. There appears to be a much higher rate of sexual acquisition of HCV in HIV-positive men who have sex with men than in HIV-negative heterosexuals (see the HCV Transmission Section). One prominent researcher I interviewed believes that having herpes lesions may greatly increase the risk of HCV transmission through sex; this may be a factor explaining the preceding observation.

Treatment of HIV in People Coinfected with HCV and HIV

In many clinics, HIV is under-treated in people with HCV and HIV infection. This is in part due to unjustified fears about using protease inhibitors (PIs) in people with HCV.

While there are some legitimate concerns about the potential increased liver toxicity of PIs in people infected with HCV, several studies, as reviewed below, now show that people coinfected with HCV/HIV can be safely and effectively treated with HAART.

Possible Mechanisms by Which HAART may Worsen Liver Function Tests in People with HCV

- PIs may cause additional direct liver toxicity or elevated plasma levels in people with HCV.
- The "immune reconstitution syndrome" may worsen the liver damage associated with HCV infection.
- HAART may result in increased production of HCV RNA.

In the first scenario, PIs may be more hepatotoxic in people with HCV, either due to elevated blood levels of the PIs, or enhanced toxicity at normal blood levels. Rutschmann reported transient increases in HCV RNA and liver enzymes in a study of 19 HCV/HIV coinfected people treated with PIs (nine on ritonavir, seven on indinavir, three on ritonavir plus saquinavir). However, HCV RNA values returned to pretreatment levels within 17-32 weeks (Rutschmann 1998). Zylberberg and colleagues treated 22 HCV/HIV coinfected people with HAART. (The regimens contained indinavir in 19 people, ritonavir in 2, and saquinavir in 1.) They observed no significant changes in liver enzymes or HCV RNA over a mean follow up of nine months; however, they did not perform serial liver biopsies to assess potential liver changes associated with the increased CD4 cells and decreased HIV RNA (Zylberberg 1998a). Another recent report studied 22 patients with HCV/HIV coinfection and found that after 24 months of HAART, 20/22 people had undetectable HIV RNA, but that there was no significant change in HCV RNA levels, although 3 patients had a transient increase in HCV RNA (Albizreh 1999).

Sulkowski observed increased liver toxicity with ritonavir in HIV-positive people, compared to other protease inhibitors. The increased liver toxicity seen in this series and associated with ritonavir use may have been partly due to a higher incidence of people with HCV (52%) in the study. The rate of severe liver toxicity with the use of PIs in people with HCV infection was 12.2% (Sulkowski 2000c).

Hepatotoxicity (grade)	Ritonavir	Other PI	NRTI*

0	33%	55%	63%
1 or 2	34%	36%	30%
3 or 4	32%	9%	7%
* NRTI = nucleoside reverse transcriptase inhibitor			

Sulkowski, however, concluded that:

> Although hepatotoxicity may be more common in persons with chronic viral hepatitis, these data do not support withholding protease inhibitor therapy from persons coinfected with hepatitis B or C virus. (Sulkowski 2000c)

There are also some reports of increased toxicity of nucleoside reverse transcriptase inhibitors (RTIs) in people with HCV/HIV coinfection. One retrospective review of 61 people reported that 39% had some evidence of increased liver toxicity of RTIs, defined as at least a doubling of serum alanine aminotransferase (ALT) and a 50% decrease within 14 days of stopping the drug (Hernandez 1999).

Additionally, there are some data demonstrating that blood levels of PIs may vary significantly in people with HCV, suggesting that therapeutic drug monitoring (TDM) may be useful in this population. Ritonavir levels have been shown to be higher in HIV-infected people with underlying liver disease, possibly necessitating a lower dose (Hsu A, 1998). Zilly observed that while HAART was generally well tolerated in people with HCV infection, there was a wide variation in blood levels of ritonavir, saquinavir, and indinavir. He recommended the use of TDM, or measuring of PI blood levels, to determine the correct dosing in people with chronic liver disease (Zilly 1999). The second possible mechanism by which HAART may worsen liver function in HCV/HIV coinfected people is via an immune reconstitution syndrome, associated with increased CD4 cells, as is seen in some people with prior TB, MAC, and CMV infection when HAART is begun. The immune reconstitution syndrome can result in a transient flare, or worsening, of symptoms at sites of infection with tuberculosis (TB), mycobacterium avium complex (MAC), cytomegalovirus (CMV), herpes simplex viruses 1 and 2 (HSV-1 & HSV-2), and varicela zoster virus (VZV) (Sepkowitz 1998; Freeman 1988). This flare is due to increased immune activity at sites of prior infection, not reactivation of the infection itself. Since at least some of the liver damage from HCV infection is due to the immune reaction to HCV, the strengthened immune system could worsen the hepatitis. (See the "HCV Pathogenesis" chapter for a review of the evidence supporting the premise that the immune response is, in part, the cause of liver damage in people with HCV infection.)

John and colleagues studied three HCV/HIV coinfected people who developed acute hepatitis when a PI-containing HAART regimen was begun. The hepatitis did not correlate

with changes in HCV RNA, and liver biopsy was suggestive more of an HCV immune-mediated response rather than of PI toxicity; however, cellular immune responses to HCV were not studied in these people (John 1998). A French group reported that the increased liver enzymes occurring in people on HAART were due to the enhanced immune response in people who had HIV RNA levels below the limit of detection, and that the changes in liver enzymes did not correlate with changes in HCV RNA values (Gavazzi 1999). Another French group, however, reported a 2.5% (5/206) incidence of PI-associated hepatitis which they could not correlate with immune reconstitution, changes in HCV RNA levels, CD4 counts, or specific PIs (Zylberberg 1999).

The third possible mechanism by which HAART may worsen liver function in HCV/HIV coinfected people is that HAART may cause increased HCV RNA production, which is observed in some people (Vento 1998). How often this occurs, and why it occurs, is not known. It is also not known whether there is enhanced liver damage as a result of the increased HCV RNA. It seems counterintuitive that improving the strength of the immune system would result in a greater production of hepatitis C virus. Mir observed that people on both PI-containing and non-PI-containing anti-HIV therapy had higher levels of HCV RNA than HCV/HIV coinfected people not on HAART (Mir 2000). Also, there are anecdotal reports of people with non-detectable HCV RNA prior to HAART experiencing significant increases in HCV RNA soon after administration of HAART. Since this phenomenon is observed fairly early after the initiation of HAART, there may be some direct interactions with HAART and HCV that are not currently understood. These phenomena have not been well studied in clinical settings.

There are also data suggesting that immune system recovery associated with HAART may also improve the ability of the immune system to control HCV replication and the resultant liver damage. Benhamou and colleagues reported that projected rates of liver fibrosis, or scarring, decreased significantly when PI therapy is used to treat HIV. Patients who received PI-containing HAART had a lower fibrosis progression rate. This report is limited due to being a retrospective study, with potential selection bias in terms of which patients were thought healthy enough to receive PI-based regimens, as well as some questions about the linear model used to project liver fibrosis progression rates. It is not at all clear why PI-based HAART regimens would result in less fibrosis, compared to non-PI-containing HAART regimens, which are equally effective at suppressing HIV RNA and improving CD4 cell counts. Nonetheless, these reports suggest that the treatment of HIV with HAART may reduce HCV progression rates and liver fibrosis (Benhamou 1999a; Bochet 2000).

The unjustifiable exclusion of people with HCV from many HAART trials has resulted in an unacceptable lack of data to address the above issues. As a result of this exclusion, important leads into the mechanisms of the immunologic and non-immunologic control of HCV replication, and the mechanisms by which HCV actually causes liver damage and fibrosis, have not been pursued. There are a considerable number of ways in which people with HCV have been excluded from many HAART trials, including: outright exclusion of people who have HCV infection; unnecessary limitations on pretreatment liver function test abnormalities; unnecessary exclusion of many active substance users/abusers; inaccurate

perceptions about the suitability of HCV/HIV coinfected people as study candidates; and exclusion of people on methadone. Unless there is a scientifically valid reason to exclude people with HCV infection from HAART trials, they should be included.

Treatment of HCV in People Coinfected with HCV and HIV -- General Considerations

In many clinics, HCV infection in HIV-positive people is rarely treated. Many hepatologists and pharmaceutical companies have chosen to focus HCV trials exclusively on HIV-negative people. This is due, in part, to the perception that: 1) HCV is more difficult to treat in HIV-positive people; 2) toxicities (namely hematological) will be greater in HIV-positive people; and 3) HIV-positive people have a shortened life expectancy and deaths on a study (even due to HIV-related causes) would tarnish study results. Thus, pharmaceutical companies are reluctant to test new therapies in people in which they fear their product may not perform very well.

Another problem in treating HCV/HIV coinfected people is that there does appear to be some potential for increased toxicity due to ribavirin (RBV) in people who are HIV-infected (see below). Some studies have reported significant rates of anemia and decreased CD4 counts in people treated with interferon (IFN) and RBV. It is unclear if this may be a result of HIV infection itself, enhanced toxicity due to some drugs used in HAART regimens, or too high a dose of RBV. Due to some early bad toxicity experiences, some clinicians are reluctant to treat HIV-positive people with IFN and RBV; however, several studies have now demonstrated that many people do well with this treatment regimen, as discussed below.

One researcher interviewed said that he had been involved in a dosing study conducted by Schering which was never published because they believed it showed that RBV at a dose as low as 600 mg was equally effective to the high doses currently recommended. If this is so, TAG believes that this is reprehensible, in that people may be needlessly exposed to potentially life-threatening toxicities so that a company can increase its profits. We call on Schering to make public all significant unpublished data they have from RBV-dosing trials ever conducted.

There is a critical need for much larger trials to be conducted on the treatment of HCV in the HCV/HIV coinfected population. Unresolved questions (among many) that need to be addressed include: What is the lowest effective dose of RBV? What is the possible clinical impact of decreased CD4 cell counts? and Which HAART regimens are best when combined with HCV therapy?

Additionally, as trials yield data for HIV-negative, HCV-infected people and resolve the issues around IFN induction dosing, IFN daily dosing, the influence of HCV genotype, the efficacy of RBV with consensus and pegylated interferons, the efficacy of amantidine with IFN, etc., additional trials need to be conducted in HCV/HIV coinfected people to determine if the results are applicable to this population. TAG recommends that HCV treatment trials stratify for HIV-infection and enroll both HIV-positive and HIV-negative people in all ongoing and future HCV trials in order to gather these critical data simultaneously.

Funding for such trials, however, is unlikely to be provided by industry, and local institutions have not shown much interest in conducting HCV therapy trials in HCV/HIV coinfected people. There is a need, therefore, for federally provided funding, either through the R01 process, or through the establishment of an HCV/HIV clinical trials network to support such trials. Both NIAID and NIDDK should share in the funding of such mechanisms. To date, none of the NIAID-funded HIV clinical trials networks have shown much interest or ability in conducting trials in HCV/HIV coinfected people in a timely manner.

Treatment of HCV in People Coinfected with HCV and HIV-Specific Trials

All of the major IFN trials, and subsequent trials with IFN plus RBV, excluded people who were HIV-positive. Thus there are much fewer data on how to treat HCV in HCV/HIV coinfected people. As discussed above, there simply is no scientific basis upon which to exclude people with stable HIV infection from HCV trials. Rapid pharmacokinetic (PK) or blood-level studies could be done to determine any potential adverse interactions among HCV investigational agents and HAART drugs in HCV/HIV-negative volunteers. The PK studies could also be done in real time on the first people to enroll in a new trial. In general, the response to IFN appears lower in HCV/HIV coinfected people, and not enough data are yet available to determine comparable response rates with IFN plus RBV.

IFN Monotherapy Trials in HCV/HIV Coinfected People			
Study	ETR	SR (6 months)	Comments
Aguilar 1992	21/41 (52%)	-	
Boyer 1992	4/12 (33%)	1/12 (8%)	IFN 3-5 MU tiw* X 4-6 mos.
Nardiello 1992	9/21 (45%)	27%	IFN 3 MU tiw X 6 mos.
De Sanctis 1993	-	5/20 (25%)	IFN 3 MU tiw X 18 mos.
Marriott 1993	5/9 (56%)	4/9 (44%)	IFN 9 MU Daily X 3 mos., then 6 MU Daily (Only 9/14 completed therapy)

Spanish Group 1993	4/18 (22%)	-	IFN 3 MU tiw X 3 mos., then 5 MU tiw X 9 mos.
Linarcs 1994	9/17 (54%)	-	IFN 3 MU tiw X 6 mos.
Garcia-Samaniengo 1994	38/88 (43%)	-	IFN 5 MU tiw X 3 mos., then 3 MU tiw X 9 mos.
Del Pozo 1994	43/79 (54%)	-	IFN 5 MU tiw X 6 mos.
Marcellin 1994	6/20 (30%)	3/20 (15%)	IFN 3 MU tiw X 6 mos.
Mauss 1995	3/9 (33%)	2/9 (22%)	IFN 5 MU tiw X 6 mos.
Pol 1995	7/31 (23%)	0%	IFN 3 MU tiw X 6 mos.
Soriano 1995, 1996	26/80 (33%)	18/80 (22.5%)	IFN 5 MU tiw, for 3-12 mos.
Boldorini 1997	-	1/12 (8%)	No cirrhosis on follow-up
Mauss 1998	8/17 (47%)	5/17 (29%)	Only 1 completed 4 mos. of therapy
Coll 1999	19/43 (44%)	5/43 (12%) (10 had a "sustained biologic response")	IFN 5 MU tiw, for 6 mos.
ETR = end of treatment response; SR = sustained response, tiw = thrice weekly			

The variables that correlated the best with response to IFN in almost all of the above studies were a higher CD4 count and genotypes other than genotype 1. In Mauss's study, the average CD4 count of responders was 525, versus 245 in non-responders (Mauss 1998). In Coll's study, the sustained virologic response rate was 11.6% in HIV-positive

people versus 21.8% in HIV-negative people. They noted, however, that an additional five HIV-positive people had a "sustained biologic responses," which was similar to the rate in HIV-negative people: 23.2% versus 24.4%, respectively (Coll 1999).

Anti-HIV Effects of IFN and RBV

Concerns have been raised about the potential effects of IFN therapy on HIV replication. There were several studies of both oral and subcutaneous IFN to treat HIV prior to the HAART era. Low-dose oral IFN has not been shown to have any benefit for treating HIV infection in all but one study (Katabira 1998; Wright 1998; Alston 1999). One pre-HAART, non-blinded study reported a survival advantage in non-AIDS, HIV-positive people (Rivero 1997). Likewise, subcutaneous IFN has not been shown to have any benefit on CD4 counts or changes in HIV RNA (Fischl 1997; Krown 1999). In the above-mentioned studies of injectable IFN, the increased toxicities included fatigue, muscle pain, and anemia. Marriott's 1993 study of IFN in HCV/HIV coinfected people included only people who were asymptomatic with regard to their HIV infection. There was a transient decrease in CD4 counts in people with counts above 400, and there was no change in CD4 counts in people with CD4 counts below 400. None of the people in Marriott's study developed detectable p24 antigen (the much less sensitive precursor test to RNA PCR to detect HIV in the blood) (Marriott 1993).

There have been a few trials of RBV to treat HIV infection using doses ranging from 600 mg to 1,000 mg/day. These trials showed that there was no change in CD4 counts, total lymphocyte counts, p24 antigen levels, or CD4:CD8 ratios compared to placebo (Spanish Ribavirin Trial Group 1991; Ribavirin ARC Study Group 1993). The most prominent adverse side effect observed in these trials was a mild, reversible hemolytic anemia.

Based on the increased efficacy of combining IFN with RBV in HIV-negative people infected with HCV, small pilot studies have been conducted with this combination in HCV/HIV coinfected people. There are a few concerns about the safety of RBV in HIV-positive people. The most common of these concerns are the potential for increased toxicity -- especially hemolytic anemia (destruction of red blood cells) -- and a potential adverse interaction between RBV and some anti-HIV drugs, particularly zidovudine (AZT, or Retrovir™), 3TC (lamivudine, or Epivir™), and d4T (stavudine, or Zerit™). RBV potentially decreases the intracellular activation of zidovudine, stavudine, and lamivudine (Baba 1987; Vogt 1987; Hoggard 1997; Kewn 1997); however, some early data conclude that this is not of clinical significance (Zylberberg 1998b). There is also some evidence that RBV may enhance the anti-HIV effect of ddI (Videx™) (Balzarini 1991), though more in-depth studies are needed to address these concerns.

IFN Plus RBV Trials in HCV/HIV Coinfection

Study	End of Treatment Response	Sustained Response (@ 6 Months)	Comments
Landau 1999	10/20	7/20	RBV 500-600 mg bid*, Genotype 3a had the best response
Dieterich 1999b	4/8 @ 3 mos. 5/7 @ 6 mos.	-	19/21 people were on HAART, anemia in 5/21, five discontinued therapy
Sauleda 1999	6/20	-	IFN 3 MU tiw, RBV 800-1,200 mg/day X 6 mos. Hemoglobin decreased from 15 to 13.4 gms/dl.
Weisz 2000	3 log decrease in HCV RNA	-	IFN 3 MU tiw, RBV 800-1,000 mg/day (11 patients). Compared to IFN alone (ten patients), there was a decrease in CD4 count of 300, anemia in 5/11 with RBV
Perez-Olmeda 2000	6/11	5/11	IFN 3 MU tiw, RBV 1000-1200 mg/day. All had previous IFN Rx. Seven patients discontinued therapy.
# All patients were hemophiliacs * bid: twice daily			

While the addition of RBV to IFN increases the probability of HCV RNA suppression, it also increases the risk of anemia; however, the anemia tends to respond well to both decreasing the RBV dose and to administration of erythropoietin (EPO) by injection (Weisz 2000; Dieterich 1999b).

Other HCV/HIV Coinfection Trials			
Study	Agents	End of Treatment Response	Sustained Response (@ 6 Months)
Wensing 1999	IFN plus Amantadine	1/3	-

Schlaak 1999	Interleukin-2 (1-2 MU/day)	0/7	2/7 (Occurred after cessation of IL-2)

No studies have been conducted using pegylated-interferon, with or without RBV, in HCV/HIV coinfected people, though there are several trials planned to begin soon which will evaluate consensus IFN or pegylated-interferons, with and without RBV, in coinfected individuals.

Timing of HIV and HCV Therapy in Coinfected People

Most clinicians interviewed by TAG recommend that in HCV/HIV coinfected people, HIV therapy be initiated first. While it is true that most trials have shown that people with higher CD4 cell counts respond better to HCV therapy, there has not yet been a randomized study comparing simultaneous versus sequential therapy. Following good suppression of HIV RNA and some immune reconstitution, the need for treatment of the HCV should be reevaluated. Mark Sulkowski suggested treating HCV in coinfected individuals when one or more of the following conditions exists:

- Stable HIV with good CD4 counts, where it may be possible to eradicate HCV
- Advanced liver disease, such as cirrhosis, where treatment may slow the progression of HCV liver damage
- Recurrent liver toxicity when HIV treatment is administered.
  (Sulkowski 2000a)

According to Douglas Dieterich:

> Overcoming the therapeutic nihilism toward chronic hepatitis C in HIV-positive patients remains the greatest obstacle for those patients who are co-infected. . . . Lowering the viral load with anti-HCV therapies can only benefit patients by improving liver disease, and may permit the addition of protease inhibitors, which will certainly prolong the patient's life. (Dieterich 1999a)

Hepatitis A and B Vaccination for HCV/HIV Coinfected People

Vaccination for hepatitis A and B is strongly recommended for people coinfected with HCV and HIV (CDC 1996). People with chronic liver disease can have fulminant hepatitis when infected by hepatitis A (Akriviadis 1989). In one study of 17 patients with HCV infection who acquired hepatitis A infection, seven (41%) developed fulminant hepatitis, and six (35.3%) died (Vento 1998).

There is a decreased response to the HBV vaccine after standard HBV vaccination in people infected with HIV, as measured by the amount of antibody produced to HBsAg, anti-HBs. The standard HBV vaccination program consists of three injections. Doubling the standard

course in people with suboptimal production of anti-HBs (<10 units), has been shown to increase the response rate from 55% to 90%. Most of the observed increases in HIV RNA following HBV vaccination were transient (Rey 2000). It is very important that levels of anti-HBs are measured periodically after HBV vaccination in people with HIV to assure adequate protection from future HBV infection.

Liver Transplantation for HCV/HIV Coinfected People

Until very recently, only the University of Pittsburgh had performed any liver transplants for people who had liver failure and/or cirrhosis from HCV who were also HIV-infected. Historically, the refusal of almost all transplant centers to perform liver transplants in this population was justified due to the very poor prognosis due to HIV infection. With the advent of HAART, however, this blanket exclusion is no longer justifiable. Now many transplant centers offer the rather weak justification that the safety of immunosuppressive drugs in HIV-infected people is not known. Several hepatologists, off the record, told TAG that they believe a major reason for many transplant centers' refusal to perform liver transplants on HCV/HIV coinfected people is that the transplant surgeons at their institutions do not want operate on people who are HIV-positive.

While it is true that there are very limited data available on the use of immunosuppressive therapy in HIV-positive people, there is only one way to gather such data. Just Do It! The outcome of not performing transplantation in a person who is dying of liver failure is certainly well-known. At the University of California-San Francisco (UCSF), the most common cause of death now in their HIV clinic is liver failure due to HCV (Wright 1999). With HAART, the risks of immunosuppression post-transplant probably will not be significantly different than in the HIV-negative HCV transplant population. There simply is no scientific justification for the continued blanket refusal of most transplant centers in the U.S. to consider HIV-positive people for liver transplantation.

UCSF has obtained $1 million funding from the state of California to perform a limited number of liver transplants in people who are HIV infected; however, these patients will only have access to "low viability" livers (i.e., those rejected for transplantation in HIV-negative people) (Wright 1999; Wickware 2000). In addition, John Fung of the University of Pittsburgh, where six HIV-positive people have already received kidney transplants, has submitted a protocol to the NIH to study liver transplantation in HCV/HIV coinfected people (Wickware 2000).

National leadership, advocacy, and perhaps some creative lawyering are needed to address this ongoing discriminatory policy at most major transplant centers.

Obstacles to Treatment (Demographics, Local Communication, and Institute Factors)

Rarely are infectious-disease physicians and hepatologists in the same clinic. People are frequently bounced back and forth between HIV clinics and liver clinics, with each physician saying, "When your other infection is under control, then I will treat you." In other words, "You go first," with the result that the person receives treatment for neither

HIV nor HCV. There is an urgent need for much better communication and interaction between infectious disease providers and hepatologists; ideally, both seeing the HCV/HIV coinfected person together. Because there have been so few trials of treatment for HIV and HCV, there are few data on which to make any recommendations regarding whether treatment should be initiated in stages, which viral infection should be treated first, or whether treatment should begin simultaneously. Such a treatment-strategy trial is desperately needed.

At the national level, there are overlapping interests at the National Institutes of Allergy and Infectious Diseases (NIAID) and the National Institute of Diabetes, and Digestive and Kidney Diseases (NIDDK) contributing to the lack of conduct of clinical trials in the HCV/HIV coinfected population. People in leadership positions at both institutes feel that their institute should be have control over the design and funding of clinical trials for HCV/HIV coinfected people.

Clearly, there are some "turf" issues at both the local and national levels that need to be promptly resolved so that the trials necessary to address the complex challenges of treating the HCV/HIV coinfected person can be funded and conducted.

Hepatitis B Virus (HBV) and HIV Coinfection Hepatitis B Virus (HBV) and HIV Coinfection

There is relatively little medical literature that addresses the natural history and treatment of HBV/HIV coinfection, and almost none that deals with the management of HBV/HCV/HIV coinfected people. In one study, however, HIV infection was shown to result in a higher rate of HBV replication and a higher risk of cirrhosis in people with HBV/HIV coinfection (Colin 1999). This study included only homosexual men with no HCV infection, no prior therapy for HBV, and no history of intravenous drug use.

Characteristics Associated With Cirrhosis	
	R Relative Risk of Cirrhosis
HIV-positive	4.21
Age (per year)	1.14
Alcoholism	7.08

Duration of HBsAg positivity	1.08
HBeAg positivity	0.20
(Colin 1999)	

The rate of progression of HIV does not appear to be significantly influenced by HBV infection. However, the rate of spontaneous conversion from HBeAg to anti-HBe appears to be lower in HIV-positive people (Gilson 1997). In a study of hemophiliacs coinfected with HBV and HCV, HIV infection was associated with a dramatic increased risk of end-stage liver disease (ESLD), which developed in over twice as many HIV-infected people, compared to HIV-negative, HBV/HCV coinfected hemophiliacs (Ragni 2000). The above studies do not reflect the potential impact of HAART on the adverse effects observed associated with HBV/HIV and HBV/HCV/HIV coinfection. Whether HAART will minimize, or reverse, the poorer prognosis of HBV and HCV infection associated with HIV coinfection remains to be determined.

Effect of HIV on HBV/HCV Coinfected Hemophiliacs		
	HIV-Negative	HIV-Positive
ESLD at age <38	0/7	6/12
Overall ESLD	7/107 (6.5%)	12/92 (13.5%)
Time to ESLD since HIV infection	7.5 years (median)	
ESLD = end-stage liver disease		(Ragni 2000)

Treatment of HBV in HBV/HIV Coinfected People

Nucleoside Analogues

Currently, there are relatively few treatment options for chronic HBV infection in HBV/HIV coinfected people; however, some anti-HIV drugs, the nucleoside analogues, also have the ability to suppress HBV replication, at least for some period of time. These drugs include 3TC (lamivudine, or Epivir™) and adefovir (Preveon™).

HBV develops resistance to 3TC frequently in HBV/HIV coinfected people (Dore 1999; Wolters 1999; Batisse 1999; Benhamou 1999c; Batisse 2000). The most common mutation seen associated with HBV resistance to 3TC is at the 550 position, in the YMDD region of HBV DNA polymerase gene (Batisse 2000; Benhamou 1999c; Thibault 1999).

Response to Lamivudine in HBV/HIV Coinfected People and the Development of HBV Resistance

	HBV DNA Response	Resistance Development	Follow-up Period
Dore 1999	Median 2.7 log decrease in HBV DNA	-	52 weeks
Benhamou 1999	57/66-HBV DNA undetectable after 2 mos., 47% after 2 years, 9% after 4 years	20% per year	-
Batisse 2000	44/44-HBV DNA undetectable after 6 months	11/44	18 months (mean)

Several reports have documented a worsening of HBV infection in HBV/HIV coinfected people when either HBV resistance developed to 3TC, or 3TC was discontinued (Altfeld 1998; Wolters 1999; Bessesen 1999). Altfeld described a person who had a worsening of HBV when lamivudine was stopped. Wolters reported two people treated with lamivudine who had a worsening of their HBV infection; one with the developed resistance to lamivudine and the other when lamivudine was stopped. Bessesen described five people who had flares in their HBV infection when either lamivudine was stopped, or resistance to lamivudine developed. It is not clear from these few case reports if there is any benefit to continuing lamivudine once HBV resistance has developed; i.e., is there any clinical benefit from drug pressure that results in a less fit virus, as has been suggested with people with multidrug-resistant HIV?

Longer follow-up data are needed to determine the importance of both immune restoration and HBV mutations on cirrhosis incidence and clinical end-points. Studies are needed to assess whether combinations of new nucleoside analogues would be more effective than lamivudine monotherapy for long-term suppression of HBV replication in both HIV-infected and non-HIV-infected patients (Benhamou 1999c).

These important concerns need to be addressed in clinical trials, as HBV and HIV resistance to lamivudine frequently develops, and it may be dropped out of secondary or tertiary HAART regimens.

Adefovir (Preveon™), a nucleotide analog, has been discontinued by Gilead from further development as a treatment of HIV in the U.S. due to problems with renal toxicity at doses of 60 mg and 120 mg a day. (On November 1, 1999 the FDA Antiretroviral Drug Advisory Committee voted not to recommend Gilead's application for accelerated approval of adefovir, at the requested dose of 60 mg a day, for the treatment of HIV.) Adefovir does, however, appear to inhibit HBV replication at doses of 30 mg, or possibly even lower. There is one 28-day adefovir trial involving 20 HBV/HIV coinfected people; 15 received 125 mg of adefovir a day, and 5 received a placebo (Gilson 1999). HBV levels fell in all people receiving adefovir, but rose after the drug was stopped, following the 28-day study period. Trials are ongoing to evaluate adefovir for the treatment of HBV, investigating dosing, long-term safety, and efficacy. Eison has reported a person who had HBV/HIV coinfection, with HBV resistant to 3TC, who subsequently had good HBV suppression on the combination of adefovir and abacavir (Ziagen™) for 22 weeks of follow-up (Eison 1999).

Another anecdotal report detailed resolution of chronic HBV infection after treatment of HIV with a ritonavir-containing regimen, though it is difficult to know from this single case report whether the improvement in HBV was related to the treatment for HIV or not (Velasco 1999).

There is a case report in the literature of a flare-up of HBV two months after initiation of HAART including stavudine (d4T), didanosine (ddI), and ritonavir, thought to represent disease reactivation induced by a strengthened immune system (Vullo 1998). How often this phenomenon occurs is unknown, but it may represent the same immune reconstitution syndrome discussed earlier.

Interferon (IFN) Interferon-?

In the early 1990s, there were a few small pilot trials evaluating IFN therapy for HBV/HIV coinfected people which suggested that IFN may be useful (Marcellin 1993; Wolfel 1994; Di Martino 1996); however, the response rate of HBV to IFN therapy appeared to be lower in HIV-coinfected people: only about 37% clearance of HBV DNA with IFN, compared to a spontaneous clearance rate of 17% in HBV/HIV coinfected people (Lane 1994).

There have been two larger trials of IFN therapy for HBV/HIV coinfected people. Zylberberg treated 25 HBV/HIV-coinfected people with IFN-alfa 2a, 6 MU tiw subcutaneously for six months. Nine of the 25 people (36%) had serum HBV DNA decrease to non-detectable levels and were considered responders; only one reappeared after therapy was completed. In a comparison group, HBV DNA spontaneously became nondetectable in only 3/18 (16.7%). There was not a correlation observed with HBV DNA response and CD4 counts (Zylberberg 1996a). Another trial of IFN (5 MU, tiw, for six months) in 26 HBV/HIV coinfected men, treated between 1987 and 1996, has also been reported. Seven of 26 (27%) became HBV DNA-undetectable during therapy. The only factor found to be associated with loss of HBV DNA, and conversion to anti-HBe, was a high pretreatment level of serum alanine transaminase. The CD4 count did not correlate with response to IFN therapy (Di Martino 2000). IFN may be a reasonable treatment for people with detectable HBV DNA levels who have developed resistance to lamivudine, regardless of CD4 cell counts.

There remain many unanswered questions about the treatment of the HBV/HIV coinfected person concerning optimal agents to treat chronic HBV infection, the long-term efficacy of those agents, resistance, cross-resistance, and the potential dangers of discontinuing therapy, once it has been initiated. Hopefully, much-needed trials will be conducted promptly to address these many vital questions.

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Current Opinions & Controversies in Hepatitis C Virus Infection

Over 40 hepatitis and infectious disease researchers, clinicians, primary care physicians, government heath administrators, industry representatives, and patients with viral hepatitis were interviewed by telephone or in person. They were all asked about their work and their thoughts on the current state of hepatitis C virus (HCV) research. Many were asked about their recent or upcoming articles which provide a basis for our current understanding of the epidemiology, pathogenesis, natural history and treatments used on patients with HCV or hepatitis and HIV coinfection. They were asked questions in three broad areas: 1) epidemiology; 2) natural history and prognostic factors; and 3) treatments.

Specific comments from those interviewed are unattributed. The assurance of anonymity allowed individuals to relate sensitive issues that they may not have otherwise.

I. Epidemiology & Risk Factors for Transmission of HCV

A. Do you think that we know the exact prevalence of HCV in the United States?

Some expressed their concern about the estimated prevalence of HCV in the U.S. They believe the CDC's NHANES III epidemiology study may have underestimated the number of people infected because they did not use intravenous drug use (IVDU) as a surrogate for HCV infection.

Infectious disease doctors who treat people with HIV/AIDS said that they only began widespread screening of their patients for HCV two to three years ago, after the advent of highly active antiretroviral therapy (HAART). The recent epidemiology data documenting that 35% to 90% of HIV-positive patients are coinfected with HCV motivated them to use HCV testing as a routine part of clinical practice.

There was concern that we will see a dramatic rise in the HCV epidemic over the next ten years. Many individuals underwent blood transfusions before 1989 or engaged in IVDU but have not been tested for HCV antibodies. A large percentage of these unidentified asymptomatic individuals with HCV will soon become symptomatic.

B. Do you believe that HCV is sexually transmissible?

A majority admitted this is a controversial subject, yet only a few felt certain that sexual transmission of HCV exists. Most of the old-guard hepatologists said that sexual transmission was not a risk factor and cited studies which documented no sexual transmission in monogamous heterosexual couples. However, some infectious disease doctors or gastroenterologists who treat HIV/HCV-coinfected patients have a strong conviction that sexual transmission of HCV exists. They explained that after hours of discussion with patients (mainly homosexual men) on HCV transmission and possible IVDU, they felt comfortable in believing that approximately 10% had no other risk factors except high-risk sexual behavior with multiple partners.

Individuals with HCV and HCV/HIV coinfection eagerly want an answer to this question because they are unsure about the risk of HCV transmission during anal intercourse. A few admit to no condom use with consenting partners and question whether they are putting others at risk.

C. Why did it take so long to recognize the seriousness of HCV/HIV coinfection?

Many AIDS clinical researchers said they were fully aware that many of their HIV-positive patients were coinfected with HCV, yet for those who were HCV-asymptomatic, the first priority was to control the HIV viral replication, immunosuppression and life-threatening opportunistic infections. In the 1980s and mid-1990s, most believed that their patients would die from HIV-related complications years before HCV would cause symptomatic liver disease.

Now that their HIV-positive patients are living longer on HAART, AIDS clinicians and researchers said that they felt the need to explore treatment options and initiate coinfection studies.

II. Natural History of HCV Infection

A. Can individuals with HCV drink alcohol?

There was great concern about alcohol usage in HCV-positive patients. Some were quick to remind me that heavy use of alcohol was one of most significant risk factors for disease progression yet felt uncomfortable defining what "heavy alcohol use" was. Most felt the need to tell their HCV-positive patients to abstain from alcohol. All agreed that this needs further study.

Many of the European hepatologists discussed their concern about heavy alcohol use in their HCV-positive patients with a past history of IVDU. They said that many patients had conquered their drug addiction but were using excessive amounts of alcohol (possibly as a coping mechanism) and ruining their liver. I was told that patient advocates like myself should openly discuss the deleterious effects of alcohol with HCV-positive patients.

B. Do you think that HCV RNA levels affect the natural history of HCV infection?

No one felt that HCV RNA was a predictor of liver disease progression and many cited seminal natural history studies. I was reminded that in the absence of treatment, host factors (i.e., gender, age at infection) are the strongest determinant of liver disease progression. Many were quick to note that a lower level of HCV RNA is preferable if one is considering treatment.

With regard to HIV/HCV coinfection, many pointed out that HAART has the tendency to raise HCV RNA levels, but it should only be a concern if the coinfected patients goes on to initiate HCV therapy.

C. Do you believe that HCV patients with genotype 1 are at increased risk for liver disease progression and/or death?

Most all who were interviewed felt that in the absence of HCV therapy, genotype 1 had no bearing on the natural history of HCV infection.

D. Is the natural history of HCV infection worse in HIV/HCV coinfected patients compared to HCV patients without HIV?

Answers to this question were mixed. Those unfamiliar with treating coinfected patients cited data documenting that coinfected patients had faster liver disease progression. HIV clinicians also believed the data, but admitted that most of the studies were conducted before the advent of HAART. There were those who said that control of HIV viral replication and halting immune suppression may put both types of patients on a level playing field. Nonetheless, most agreed that large natural history studies are needed to answer this question.

III. Treatment of HCV Infection

A. Do you insist on a liver biopsy before treating a patient with HCV?

There were some who insisted on having the findings of a liver biopsy, and said that they would not treat a patient unless one was performed. However, many would treat in the absence of a liver biopsy and felt comfortable with simply knowing the patient's lab values (i.e., ALT, HCV RNA, albumin). A few claimed that they could roughly predict their patient's liver histology grade and stage with the right lab values.

B. Why are so many hepatologists unwilling to treat HIV/HCV coinfected patients?

One researcher said that a majority of hepatologists believe that HIV infection is something outside their expertise and because the field is changing so rapidly, it is difficult to keep up-to-date. He also said that hepatologists have difficulty with HIV patients being on so many medications and felt that most would want to take patients off all drugs to see exactly how the liver was functioning on its own. A number of researchers did tell me that they were encouraging fellows to explore HIV/HCV coinfection research. Many believe that a combined ID/GI approach will offer the patient the best care.

C. Should all patients with HCV be treated with combination therapy?

The answers were surprisingly mixed on this question. Many did not see the harm in treating all of their patients with a 6-month course of IFN/RBV and seeing what happens. They believed that HCV is a progressive disease and if left untreated, it would eventually get worse. Other clinicians were much more conservative in their approach to treating HCV and would not recommend therapy unless the patient had at least stage 1 fibrosis. I was reminded that less than half of HCV-infected patients progress to cirrhosis and therapy is only effective in one out of three patients. Many felt comfortable monitoring their patients

over time to decide when treatment might be warranted. More effective and less toxic therapies might become available when the patient finally needs therapy.

D. Do you believe the retrospective Japanese studies which document a decrease in hepatocellular carcinoma (HCC) and death in HCV patients with IFN?

An overwhelming majority of U.S. and European researchers did not believe the data, especially that which demonstrated a benefit in IFN non-responders. Their reasons were that all the data are retrospective and riddled with methodological flaws.

Many are excited about the NIDDK's HALT-C study and hope that it will tell us whether or not long-term IFN therapy decreases the risk of HCC.

E. Is there a benefit to maintaining an IFN non-responder or relapser on IFN?

Some felt strongly that IFN has antifibrotic properties and that those HCV patients with cirrhosis or transition to cirrhosis might need something to halt liver disease progression. If the patient could reasonably tolerate therapy, they saw no problem with recommending continuation of IFN.

Many researchers said that more work needs to be done to find anti-fibrotic drugs which would be active in patients with HCV.

F. Do you feel comfortable treating HIV/HCV coinfected patients?

Most of those interviewed said that they feel comfortable treating coinfected patients and have done so for many years. They believe that IFN or IFN/RBV response rates are similar in both patient populations. Nonetheless, many believe that heavily immunosuppressed HIV-positive patients (i.e., those with <200 CD4 cell/m3) fare worse.

Just about all clinicians who treat coinfected patients said that they preferred to have them initiate HAART first, get the HIV viral load undetectable and CD4 cells up before beginning HCV therapy. Most of the European clinicians felt comfortable working as a team with infectious disease doctors at their institutions.

G. Should HCV patients on a treatment study have access to their HCV viral load?

Compared to patients, researchers and clinicians did not have strong feelings one way or the other. Patients believed that they have a right to timely access of their HCV viral load so that they can discontinue therapy at 3 or 6 months if HCV RNA is detectable.

H. How serious is the depression and emotional unrest in IFN-treated patients?

Quite a few clinicians believe that IFN takes a serious psychological toll on their patients. Some advise patients to initiate antidepressants or even consider a short-term leave of absence from work.

Research and Policy Recommendations

1. The CDC should further investigate the role of HCV sexual transmission in MSM.
2. The CDC should update its 1998 HCV recommendations to suggest HCV testing for all persons with HIV/AIDS.
3. More research should be conducted to completely understand the immunologic responses associated with control of HCV infection.
4. The NIAAA should commence studies on the effects of alcohol in patients with HCV. The findings should be widely distributed to patients and community physicians in a timely manner.
5. Large natural history studies should be initiated to determine the current natural history of HIV/HCV coinfected individuals in the era of HAART.
6. The NIH ICDs (i.e., NIAID, NIDDK, NHLBI) should issue multiple RFAs for cross-training of fellows in hepatology and infectious disease/HIV research.
7. The NIH's Office of AIDS Research should make available some of its discretionary funding for basic and clinical research on HIV/HCV coinfection.
8. The NIH should explore the desirability and feasibility of a Hepatitis Clinical Trials Network. The network would carry out Phase I to IV clinical studies with nested basic science research.
9. Future HCV treatment trials should stratify for HIV serostatus and enroll both HIV-positive and HIV-negative people in order to gather these critical data.
10. HCV treatment should be mandated in all state and federal prison systems.
11. Transplant centers in the U.S. should consider HIV-positive people for liver transplantation.
12. HCV patients must have access to their HCV RNA levels at timely intervals (e.g., week 24) while on HCV treatment studies.
13. Schering Plough must unbundle Rebetron™ so that ribavirin can be purchased separately.
14. Research should be conducted to determine the lowest effective dose of ribavirin to minimize unnecessary toxicity.
15. All 50 U.S. States should add ribavirin to their Medicaid and ADAP formularies.
16. Industry should conduct drug interaction studies of anti-HIV drugs in HIV/HCV coinfected people while drugs are in development so that potential hepatotoxicity and drug interactions are defined prior to approval.
17. The FDA should grant Hoffmann-La Roche's PEG-IFN NDA a "priority review" because of the unmet medical need for therapies for HCV patients with cirrhosis.
18. HCV treating physicians should fully explain the risk and benefits of IFN/RBV combination therapy with their patients as well as estimates of treatment response according to host and viral characteristics.
19. Industry must actively recruit African Americans in all phases of HCV clinical trials. These studies should have the statistical power to assess racial differences in viral clearance and response rates.
20. Hepatitis treatment advocates should be included in all facets of NIH decision making about hepatitis clinical and basic science research, including protocol development, scientific agenda committees and grant reviews.

Clinician's Response

Jeffrey Schouten, M.D.

I have read this TAG report on Hepatitis C and as a clinician I was very happy. Not because it was the perfect book with a perusal review of all evidence-based articles. Not because I found my own articles in the references. Not because I share most of the conclusions. I like it probably because it is well balanced between landmark studies and also stimulating small articles and abstracts. One explanation could also be that the pure academic hepatologist needs fresh spirit from the HIV world where there was (is) an emergency of efficacy.

The natural history chapter reminds us that liver fibrosis progression rate is the major surrogate endpoint for disease severity. HCV is a curious disease with a major aging phenomena. Infected at 5 years of age or at 40 years, the fragile subject will have cirrhosis at 50 years of age. This must be explained to the patient.

I have also liked the discussion of sexual transmission. There is a very pragmatic message here. We all agree to reduce the anxiety among spouses, saying that the risk is minimal and a condom is not mandatory. But we also have to say that the exposure to blood is possible during sexual intercourse. The examples of the authors, taken from the HIV experience, are excellent. One could also add the possible role of herpes infection. Therefore, condoms must be recommended for sexual intercourse during certain periods, especially in the presence of ulcerations or for anal intercourse.

For the chapter concerning HCV-RNA quantification, the HCV clinician would emphasize that HCV viral load has not the same importance that HIV viral load has in the management of HIV disease. As stated several times by the authors, HCV viral load is not associated with the severity of the disease (i.e., fibrosis progression rate). Also in treatment strategy, we are very disappointed by the predictive values of quantitative PCR. Indeed, there is a correlation between the 4-week impact of treatment and the sustained response, but this correlation is too weak to permit 100% positive or predictive values. Furthermore, the prediction made by viral kinetics for patients treated with 24 weeks of an IFN-ribavirin combination regimen are false if patients are treated for 48 weeks. Maybe we have to remind ourselves that HCV is not a blood disease but a liver disease. Blood kinetics are perhaps unrelated to liver kinetics.

The chapter concerning co-infection with HIV raises one very important clinical problem: the need for liver transplantation of HIV-HCV co-infected patients who are dying from liver insufficiency, hemorrhage or liver cancer. Trials are certainly needed, but I am convinced that we now have the skill to manage both viruses after the transplantation. Too many young patients are dying these days. Just do it . . . ?

The chapters on therapies are also very good. Physicians must also know that interferon is very effective as an antifibrotic agent. While waiting for new anti-viral drugs, non-responders can be treated with interferon alone in order to reduce fibrosis progression. In patients co- infected with HCV-HIV, this maintenance therapy must be considered in rapid fibrosers. The chapter on new therapies is particularly interesting to read. As an

experimented trialist I would temper the indirect comparisons between different PEG-interferons. We have been disappointed already by preliminary results and indirect comparisons between interferons. We know now that there are at least five independent risk factors of viral response. Therefore, only large randomized trials can prove that one PEG-interferon is better than another one. A small difference in genotype can confound any comparison. The remarks concerning patents and other industrial factors have to be explained to patients and naive doctors.

The Research and Policy Recommendations are sound and important. The call for increased basic and clinical research funding, physician and patient education, studies to answer epidemiology and natural history questions in select patient populations, and novel antiviral treatments will have a tremendous impact on the future of this disease.

In a clinical conclusion, I will certainly recommend the prescription of this report, reimbursed or not.