V. Hepatitis C Treatment

Summary

The current standard of treatment for hepatitis C virus (HCV) is a combination of two drugs: pegylated interferon and ribavirin. The virological response rate, treatment duration, and ribavirin dose vary according to several prognostic factors: genotype, baseline HCV RNA (viral load), race, body weight, age, and liver histology. In one study, 48 weeks of pegylated interferon plus ribavirin led to treatment responses ranging from 47% to 82% (Hadziyannis 2004). Overall, approximately 50% of those treated for hepatitis C will achieve a sustained virological response (SVR), meaning that no virus is detected in the bloodstream six months after completing treatment. Whether or not an SVR is equivalent to a "cure" is a controversial matter. Treatment may be beneficial for individuals who do not achieve an SVR; some have an improvement in liver condition or a stabilization of disease progression, although the durability and clinical benefits of these improvements are unknown at present.

The decision to treat hepatitis C is a complex one. The current guidelines recommend treatment for individuals with the greatest risk of developing cirrhosis (NIH 2002). The rationale for treatment is less clear-cut for members of understudied populations. Pivotal treatment trials excluded children; the elderly; individuals with renal disease; individuals with mild or advanced liver disease; liver transplant recipients; hemophiliacs; individuals with psychiatric co-morbidities; and active drug and alcohol users. Therefore, few data exist about safety and efficacy of treatment in these populations. Studies have shown that treatment is less effective for African Americans, although the reasons for diminished efficacy are not clear. The potential benefits of treatment must be carefully weighed against the side effects, which range from uncomfortable to debilitating, and in rare instances are life-threatening. Interventions are available to minimize side effects, but more research is needed to improve the tolerability of HCV treatment. Questions about dosing and duration of therapy remain as well.

Other key concerns related to HCV therapy include access to treatment and quality of care. Treating HCV is costly; a year of therapy (not including medications to ameliorate side effects) may cost up to $40,000. Treatment is rarely available to incarcerated persons, despite a shockingly high prevalence of hepatitis C among prisoners. Hepatitis C is also prevalent among people with significant co-morbidities, including drug and alcohol addiction and mental illness; these individuals require multidisciplinary care. Primary care providers often lack adequate information about the diagnosis, care, and treatment of hepatitis C. Finally, alternative and complementary therapies, although widely used, have not been adequately researched.

Although results from three large trials of pegylated interferon plus ribavirin are available, people weighing the potential benefits of HCV treatment against considerable side effects are still without a simple answer to the key question: "Will this work for me?" An algorithm that considers individual prognostic factors (genotype and baseline HCV viral load, liver histology, baseline liver enzyme levels, age, sex, and race) does shed some light on the likelihood of achieving a sustained virological response, yet people with hepatitis C, clinicians, researchers, and advocates continue to seek information on optimal treatment and side effect management strategies while awaiting better therapies.

For information about treatment of HCV in HIV-coinfected individuals, see Chapter VII, HCV Treatment in HIV/HCV Coinfection.

Who Needs Treatment?

If the natural history of hepatitis C infection followed an identical and predictable course in each infected individual, and HCV treatment were universally efficacious, had minimal side effects and were not exceedingly costly, the question of whom to treat would become moot. Active drug users, liver transplant recipients, people with decompensated cirrhosis, HIV and/or HBV coinfection, mental illness, and other significant co-morbidities have been excluded from these trials. HCV treatment may indeed be less effective and less tolerable for those who need it most. Despite improved treatment efficacy, the side effects remain problematic. For some individuals, they may be insurmountable. The cost of combination treatment—up to $40,000 per year, not including other agents often used for side effects management—creates an additional barrier to treatment for many who need it.

The National Institute of Health's 2002 *Consensus Statement on the Management of Hepatitis C* (NIH 2002) recommends that hepatitis C treatment be offered to:

> Patients with an increased risk of developing cirrhosis. These patients are characterized by detectable HCV RNA levels higher than 50 IU/mL, a liver biopsy with portal or bridging fibrosis, and at least moderate inflammation and necrosis. The majority also have persistently elevated ALT values. In some patient populations, the risks and benefits of therapy are less clear and should be determined on an individual basis or in the context of clinical trials.

The decision to treat chronic hepatitis C is more complex for people with normal or only slightly elevated ALT values (less than two times the upper limit of normal) and symptomatic mild liver disease; individuals with advanced liver disease; those with kidney disease; the elderly; and children. More research is necessary to guide treatment decisions in these populations.

Hepatitis C Treatment: Pegylated Interferon and Ribavirin

The standard of care for treatment of HCV is a combination of two drugs: pegylated interferon alfa (taken as injections) and ribavirin (taken in pill or capsule form; a liquid form of ribavirin for pediatric use has been approved by FDA). The course of treatment may be 24 or 48 weeks, depending on the HCV genotype.

Pegylated Interferon

Interferons are cytokines (chemical messengers) that are naturally produced by white blood cells to help fight infections and inhibit abnormal tissue growth in the body. Interferon (IFN) has antiviral and immunomodulatory effects. Different types of recombinant interferon—alfa, beta, and consensus—have been used to treat hepatitis C. Interferon alfa-2a and interferon alfa-2b have been used to treat hepatitis C since 1989 (Davis 1989; Di Bisceglie 1989). The only difference between these two interferons is the amino acid at position 23, which is lysine in alfa-2a and arginine in alfa-2b.

Pegylation—the attachment of a nontoxic molecule called polyethylene glycol—keeps interferon in the bloodstream longer and at more constant levels, thus increasing the efficacy of interferon treatment while reducing the frequency of injections (Perry 2002; Reddy 2001; Zeuzem 2000). Two forms of pegylated interferon have been approved by FDA for treatment of chronic HCV: pegylated interferon alfa-2a (Pegasys®), which uses a large (40kd) branched molecule of polyethylene glycol, and pegylated interferon alfa-2b (Peg-Intron®), which uses a smaller (12kd) linear molecule of polyethylene glycol. Attachment of the PEG molecule extends the half-life of Peg-Intron® to approximately 40 hours (compared to 3.6 hours for the parent molecule); the mean half-life of Pegasys® is 80 hours, with a range from 50 to 140 hours (compared to a mean of 5.1 hours for the parent molecule). Pegylated interferon alfa-2a is given at a fixed dose and is premixed; pegylated interferon alfa-2b is dosed according to weight and must be reconstituted with sterile water before administration (the manufacturer has developed a pre-filled dosing pen to simplify the process). The most commonly reported side effects of interferon are fatigue and flulike symptoms. Other side effects include hematologic toxicities and depression. Side effects may range from uncomfortable to debilitating; in rare instances, they may be life-threatening.

Ribavirin

Ribavirin (RBV) belongs to the family of nucleoside analogs (a class of drugs also used to treat HIV, although ribavirin has no effect against HIV). By itself, ribavirin is ineffective against hepatitis C, but when it is used in combination with interferon, the combination is more effective than interferon monotherapy (Di Bisceglie 1995; McHutchison 1998; Poynard 1998). It has been speculated that ribavirin may force hepatitis C virus into "error catastrophe" by increasing mutation of hepatitis C until it can no longer replicate (Cameron 2001; Crotty 2002; Graci 2002). Ribavirin is available under the name of Copegus® (Roche), Rebetol® (Schering), and from compounding pharmacies. It is also available as a generic. Ribavirin may be given at a fixed dose based on efficacy by genotype, or dosing may be weight-based. The most frequently reported side effect of ribavirin is hemolytic anemia, which is usually reversible.

The combination of pegylated interferon and ribavirin is the most effective hepatitis C treatment to date. Approximately half of those treated will achieve a sustained virological response (DiBisceglie 2002; Fried 2002a; Glue 2000; Manns 2001).

Assessing Responses to Hepatitis C Treatment: EVR, ETR, and SVR

Treatment for HCV can be evaluated by virological, histological, and biochemical responses, and at different time points: early, at the end of treatment, and six months after completion of treatment.

- Virological response is defined as either undetectable or significantly decreased HCV RNA.

- Histological response refers to an improvement in the condition of liver tissue, assessed by a better-than-baseline histological grade (amount of disease activity) in a post-treatment biopsy.

- A biochemical response reflects liver enzyme (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) levels that have decreased to within the normal range at the end of treatment, or for at least six months after completion of treatment.

- An early virological response (EVR) is defined as either a 2 $\log_{10}$ drop (a decrease in viral load by an order of 100; for example, decreasing from 2,000,000 to 20,000 copies) in HCV RNA, or undetectable HCV RNA twelve weeks after initiating treatment.

- An end-of-treatment response (ETR) means that an individual has no detectable HCV RNA in the bloodstream upon completion of treatment; many studies report ETR. While providing useful data, ETR should not be confused with the more robust SVR, as some individuals relapse during the six-month period between ETR and SVR reports. The rate of ETR is always higher than the rate of SVR.

- A sustained virological response (SVR) occurs when an individual has undetectable HCV RNA six months after completing HCV treatment. Many consider an SVR to be a cure or at least an indication of long-term remission, though this is controversial.

- One study found no detectable HCV RNA in the serum of five individuals who had achieved SVR ten years earlier (Lau 1998), while two studies reported relapse rates among 9% to 12% of sustained virological responders after five years of follow-up (Pradat 2003; Veldt 2003).

- A non-responder is someone who does not have a significant reduction in HCV RNA levels (<2 $\log_{10}$) after a specified interval of treatment (usually 24 weeks), or who has a significant decrease in HCV RNA, but never becomes HCV-RNA-undetectable during treatment. Some non-responders may have improved liver histology after treatment (Shiffman 1997).

- Not all individuals with an end-of-treatment response will maintain a sustained virological response; individuals with an ETR, but not an SVR are referred to as relapsers.

Long-Term Follow-Up of Sustained Virological Responders

Reports of the durability of sustained virological responses to HCV treatment vary. Early reports may have overestimated the proportion of sustained virological responders who remained virus-free years later. Older, less sensitive assays may have failed to detect low levels of viremia, thus some may have initially been misclassified as sustained virological responders. Others may have been reinfected. Very low levels of replication-competent hepatitis C have been discovered in blood from 11 individuals up to five years after they achieved SVR (Pham 2004). Corresponding liver biopsy samples were not available; the impact of low-level, replicating HCV on the liver histology of these sustained virological responders is unknown. Long-term follow-up of sustained virological responders treated with standard and pegylated interferon-based regimens is needed.

Table 1. Number and Percent of Sustained Virological Responders 3.5–10 Years Later

Author & date	N achieved SVR	Duration of follow-up	Undetectable HCV RNA at follow-up
Lau 1998	5	10 years	100% (5/5)
Sim 1998	5	Median: 48.2 months (range: 23–66)	100% (5/5)
Reichard 1999	26	3.5–8.8 years	92% (24/26)
Veldt 2003	286	59 months (range: 12–20)	91% (25/286)
Collier 2000	16	Mean: 38 months (range: 6–92)	88% (14/16)
Pradat 2003	59	5–7 years	88% (7/59)

Care for Hepatitis C

> *When I went back for the [HCV test] results,… she offered almost no information at all about the virus, explaining that she "just doesn't see it" in her surgery, and handed me a brochure produced in 1991, which said that there was little in the way of treatment, that the prognosis was not good…. All of this was simply untrue in 2000, but I did not know that then.*
>
> —Lisa Waller
> *Medical Journal of Australia*

Provider Education

Not all primary care physicians are well educated about hepatitis C. Consequently, their patients receive suboptimal care and inaccurate information despite recent medical advances in hepatitis C diagnostics and treatment. In 1999, Shehab and colleagues released their landmark survey of practice patterns of primary care physicians in the management of hepatitis C. The survey included an assessment of general knowledge of hepatitis C and clinical vignettes. The surveys were completed and returned by 33% (404/1,233) of physicians in a large HMO in Michigan. Birth from a mother with hepatitis C was ranked as a significant risk factor for hepatitis C infection by 80%; 20% thought that a blood transfusion in the United States after 1994 presented a significant risk;

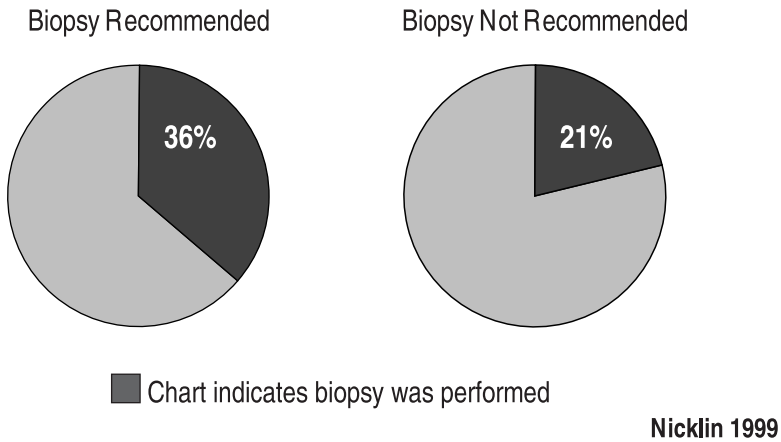
and 8% thought that casual household contact with an HCV-infected person presented a significant risk for acquiring hepatitis C. Only 2% had read the Consensus Development Conference Statement. Most respondents agreed to liver biopsy and interferon treatment if recommended by a gastroenterologist, but 72% either overestimated the response rate to interferon therapy or did not know what the response rate was (Shehab 1999).

Shehab and colleagues published results from a national survey in 2001 that assessed provider knowledge of risk factors for hepatitis C, attitudes about HCV testing, and actual management of patients with HCV. Completed surveys were received from 39% (1,412/4,000) of primary care providers across the United States. Although more than 90% were aware of the most common risk factors for hepatitis C, only 59% asked all of their patients about their risk factors for hepatitis C. Only 70% tested patients who had disclosed being at risk for hepatitis C infection, and a quarter of survey respondents did not know which treatment to recommend for hepatitis C (Shehab 2001).

Another group of researchers assessed the care received by patients with hepatitis C from an integrated medical delivery system in Philadelphia in which approximately 855 physicians provide medical care at 108 sites to about 500,000 patients. Surveys were sent to 222 physicians; 172 responses were analyzed. In addition, the medical charts of 186 individuals with hepatitis C were reviewed. Although ALT testing was frequently ordered as a part of routine medical care, 34% of physicians reported that they did not order HCV antibody testing for patients with elevated ALT levels. HCV antibody testing was ordered by only 21% of physicians with patients who disclosed parenteral (injecting) risk factors. Seventy-nine percent did not routinely test these patients for HCV. Screening for HCV antibodies was more frequently offered by physicians with practices in affluent, mostly white suburban areas; this is concerning because HCV is prevalent among African Americans and individuals with low socioeconomic status (M. J. Alter 1992).

There were substantial gaps between physicians' survey responses and the information from medical charts of 186 hepatitis C patients. Although 79% (147/186) of the HCV patients had elevated ALT levels, only 55% (102/186) had been seen by a gastroenterologist. According to their survey responses, physicians indicated that they referred 75% of HCV patients to specialty care. Only three individuals (2%) had been vaccinated against hepatitis A; only six (3%) had been vaccinated against hepatitis B (Nicklin 1999).

Figure 1. Physician-Reported Biopsy Recommendation vs. Documentation of Biopsy on Chart



Nicklin 1999

In 2003, Shehab and colleagues published another survey of the diagnosis and management of hepatitis C among patients of primary care clinics. They reviewed medical records from three groups of 229 individuals. Members of group one were HCV-antibody-positive, members of group two were HCV-antibody-negative, and members of group three had never been tested. Hepatitis C testing was initiated by the physician for just 16% (37/229) of group one and for just 10% (22/229) of group two. In group three, only 1% (2/229) had documented evidence of having had a discussion about hepatitis C with their physician. Although a majority (77%) of group one patients with detectable HCV RNA and elevated liver enzymes were referred to specialty care, almost half (40%; 24/59) of those biposied were diagnosed with bridging fibrosis or cirrhosis (Shehab 2003). These data underscore the importance of timely provider-initiated discussion of, and screening for, hepatitis C.

Guidelines for the management of persons with hepatitis C are extremely valuable. They must, however, be accompanied by initiatives for provider education to ensure the identification of and optimal care for individuals with hepatitis C.

Prognostic Factors

Coinfection with HIV

See Chapter VII, HCV Treatment in HIV/HCV Coinfection.

Genotype

Genotype is the strongest predictor of response to treatment. Genotypes 1 and 4 do not respond to treatment as well as genotypes 2 and 3, regardless of the type of interferon used (Berg 2003; Fried 2002a; S. Lee 2002; McHutchison 1998; Poynard 1998). In their meta-analysis of data from three trials of pegylated interferon alfa-2a, Lee and colleagues found a non-1 genotype to be the strongest independent predictor of SVR (OR, 4.11; 95% CI, 2.90–5.86; P=0.0001) (S. Lee 2002). A 24-week course of treatment for individuals with genotypes 2 and 3 appears to be sufficient; a 48-week course of treatment is recommended for individuals with genotypes 1 and 4 (Di Bisceglie 2002; Hadziyannis 2004).

Genotype 3 does not appear to be as sensitive to treatment as genotype 2 (Mangia 2004: Zeuzem 2003). Zeuzem and colleagues treated 224 individuals with HCV-2 or HCV-3 with 1.5 μg/kg of pegylated interferon alfa-2b plus weight-based rivavirin (800 to 14,000 mg/day) for 24 weeks. Overall, 81% achieved sustained virological response, but SVR rates were lower in those with genotype 3 (79% [143/182]) than in genotype 2 (93% [39/42]). Relapse rates were higher in genotype 3 (14% vs. 7% in genotype 2). The difference in response rates may be attributed in part to steatosis and high baseline viral load. Steatosis was significantly more prevalent in genotype 3 (P=0.003), and it was associated with a high baseline viral load (P=0.001). Steatosis of <5% was significantly associated with SVR (P=0.015) (Zeuzem 2003).

Genotype 4 may be more responsive to treatment than genotype 1. Sustained virological response rates from two studies that used 48 weeks of pegylated interferon plus ribavirin have ranged from 40% to 61% (Esmat 2003; Hassan 2003).

The viral kinetics of hepatitis C during early treatment differ depending on the genotype of HCV (A. U. Neumann 2000; Pawlotsky 2002; Zeuzem 2001). Frequent blood sampling from 12 individuals with HCV genotypes 1a, 1b, 2a, and 2b over the first 14 days of high-dose interferon revealed significant differences. Individuals with genotypes 2a and 2b had larger and more rapid decreases in HCV RNA after 48 hours than those with genotypes 1a and 1b (2.95 log copies/mL vs. 1.65 log copies/mL; $t^1/_2 = 2.0 \pm 0.5$ hours vs. $t^1/_2 = 3.0 \pm 1.0$ hours). At the end of 14 days, a significantly larger proportion of individuals with genotypes 2a and 2b had undetectable HCV RNA ($P=0.03$) (A. U. Neumann 2000). An examination of first and second-phase viral kinetics by genotype and mode of treatment (standard or pegylated interferon monotherapy) revealed more rapid first-phase and second-phase viral decay slopes for non-1 genotypes treated with pegylated interferon (Zeuzem 2001). Pawlotsky and colleagues observed less marked decreases in second-phase viral decay in genotypes 1 and 4 vs. genotype 3. At four weeks of treatment, individuals with genotypes 1 and 4 were less likely to be classified as rapid responders (individuals with decreases ≥ 0.3 log per week) (Pawlotsky 2002).

Baseline HCV RNA

A low baseline HCV-RNA level (≤ 2 million copies or ≤ 800,000 International Units) is a significant predictor of response to treatment. Numerous trials of both standard and pegylated interferon have confirmed that those with low baseline HCV RNA levels have a greater likelihood of achieving SVR (Fried 2002a; Hadziyannis 2002; Manns 2001; Poynard 1998).

The Role of Race/Genetics

In the United States, HCV is most prevalent among African Americans (see Chapter I, Epidemiology of Hepatitis C), who are more likely to be infected with genotype 1 than Whites, Hispanics, or Asian Pacific Islanders ($P<0.001$) (Blatt 2000; Jacobson 2002; Wiley 2002). It has been observed in several studies that African-Americans have impaired responses to interferon (De Maria 2002; Jeffers 2002; Kinzie 2001; McHutchison 2000; Reddy 1999; Theodore 2003). Results from a study of 472 individuals treated with either consensus interferon or interferon alfa-2b thrice weekly for 24 weeks found markedly poorer responses among African Americans than among Whites, Hispanics, and Asian Americans both during and after therapy. HCV-RNA levels were measured at baseline and weeks 0, 2, 4, 6, 8, 12, 20, 24, 36, 44, and 48. During treatment, HCV-RNA levels during treatment decreased by approximately 2.3 log in Whites vs. decreases of approximately 0.3 log in African Americans. Only 1 African-American participant (2%) achieved an SVR, while 46 white participants (12%), 4 Hispanic participants (10%), and 3 of the Asian-American participants (30%) achieved SVR (Reddy 1999).

Two efforts to increase virological response among African Americans by using high-dose interferon were unsuccessful. In one study, after 24 weeks of therapy, 26% of African Americans had undetectable HCV RNA vs. 60% of Whites ($P<0.01$). After 48 weeks, response rates among African Americans diminished to 10%, vs. 53% for Whites ($P<0.0001$) (De Maria 2002). A retrospective analysis of a treatment trial using two doses of interferon alfa-2b (3 MIU thrice weekly or 5 MIU daily) in African-American and white individuals with genotype 1 infections found similar initial responses among those treated with 3 MIU of interferon; however, when HCV-RNA levels on the high, daily-dose regimen were compared, African Americans had slower reductions in HCV

RNA than Whites (Theodore 2003).

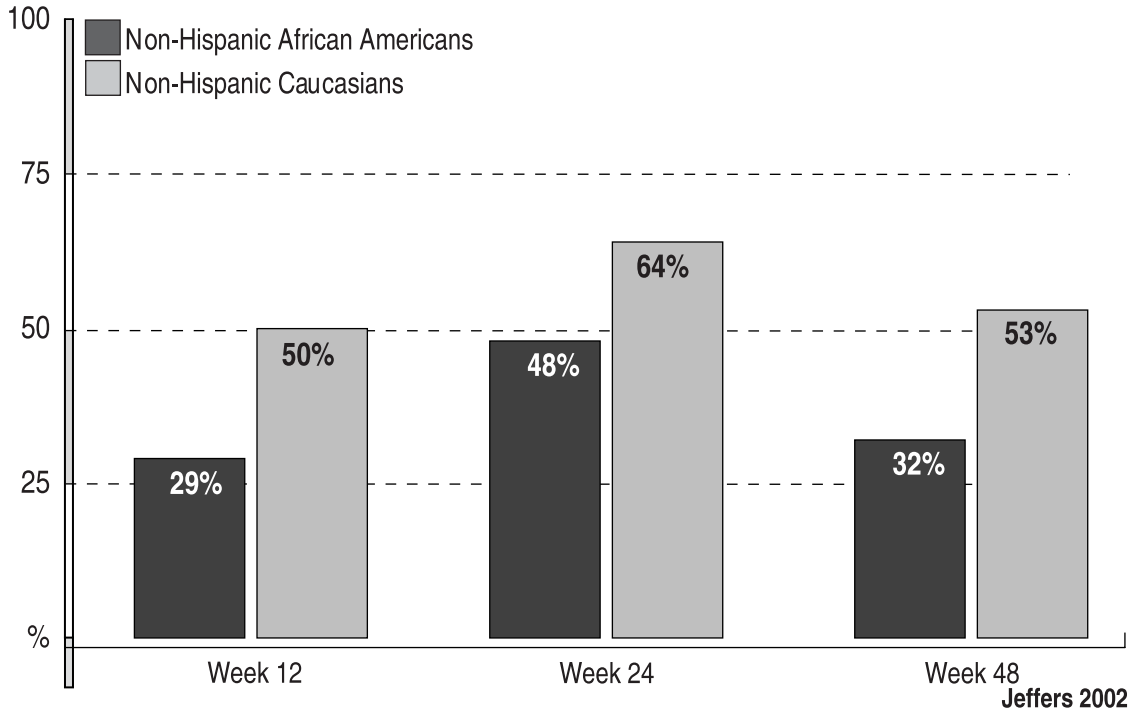
Data from two large clinical trials suggest that the addition of ribavirin increases virological response rates among African Americans. McHutchison and colleagues examined response rates from two large randomized trials utilizing four different treatment regimens. After 48 weeks of interferon monotherapy, no African-American participants achieved SVR. Adding ribavirin to interferon increased the percentage of African Americans achieving SVR from 0% to 23% (vs. 42% of Whites). Fewer than 4% (53/1744) of all participants were African Americans. Trials are rarely designed to ensure that the demographics of HCV infection in the United States are accurately reflected.

A majority of HCV-infected African Americans have HCV genotype 1 (Blatt 2000). Although genotype 1 infections do not respond to treatment as well as infections with genotypes 2 and 3, the differential response rates among African Americans cannot be attributed solely to genotype. Three treatment trials using standard interferon have reported impaired responses in African Americans with HCV genotype 1 (Kinzie 2001; Reddy 1999; Theodore 2003). Reddy and colleagues found fewer biochemical and virological response rates among African Americans vs. Whites with genotype 1 (6% vs. 34% for biochemical response rates; $P=0.001$; 6% vs. 22% for virological response rates during therapy; $P=0.038$). Kinzie and colleagues compared end-of-treatment responses of genotype 1-infected African Americans and Whites, finding that 2% (1/45) of African Americans achieved an ETR vs. 15% (5/33) of Whites ($P<0.05$) (Kinzie 2001). Although Theodore and colleagues saw similar response rates between African Americans and Whites with genotype 1 infections treated with 3 MIU of interferon thrice weekly, when the dose was increased to 5 MIU daily, Whites were most likely to have an initial response ($P<0.001$). Conversely, McHutchison and colleagues observed similar response rates among Blacks and Whites with genotype 1 infections (23% and 22%, respectively) in two large clinical trials (McHutchison 2000).

The pivotal studies of pegylated interferon had few African-American participants. Although data from subgroup analyses of these trials are available, the number of non-white participants has been too small to allow confident conclusions.

The efficacy of pegylated interferon alfa-2a plus ribavirin (1,000 mg–1,200 mg/day) has been assessed in 78 non-Hispanic African Americans and 28 non-Hispanic Whites, all with genotype 1 infections. Although sustained virological response rates among African Americans occurred more frequently in this trial than in previous studies, response rates remained greater among non-Hispanic Whites (Jeffers 2003).

Figure 2. Virological Response to Treatment in Non-Hispanic African Americans and Non-Hispanic Whites*



*Treatment was completed by 63/78 non-Hispanic African Americans and 22/28 non-Hispanic white participants.

Recent evidence suggests that some African Americans who do not achieve SVR may attain histological benefit from HCV treatment, although the durability of the improvement is currently unknown. Cassidy and colleagues evaluated histological responses from paired biopsies of 53/78 African Americans treated with pegylated interferon alfa-2a and ribavirin (1,000–1,200 mg/day) for 48 weeks. SVR was achieved by 32% (17/53) with paired biopsies. Improvement in fibrosis (≥ 1 point decrease in Knodell fibrosis score) occurred in 29% (5/17) of those who achieved SVR as well as 22% (8/36) of virological non-responders (Cassidy 2003).

There is an urgent need to investigate the contribution of additional genetic, environmental, and other factors to these differential responses, so that interventions to improve virological and histological treatment outcomes among African Americans may be developed.

A retrospective analysis of data from a multicenter HCV treatment trial and a compassionate access program in Australia and New Zealand reported that response to HCV treatment may be different in Southeast Asians. Dev and colleagues analyzed data from 70 Southeast Asian and 50 white individuals with standard interferon alfa-2, using induction/maintenance or regular dosing with 1,000–1,200 mg/day of ribavirin. Those with HCV genotypes 2 and 3 were treated for 24 weeks; all others were treated for 48 weeks. HCV genotypes 7, 8, and 9—regarded as new genotypes rather than subtypes of genotype 6 as previously thought (Tokita 1994)—were present in 33 Southeast Asians and emerged as independent predictors of an SVR (OR, 16.56; 95% CI, 4.16–18.04). SVR was achieved by 79% (26/33) of those with genotypes 7, 8, and 9. Unfortunately, because the sample size was small in this study (33 Southeast Asians with genotype 7, 8, or 9; 7

Southeast Asians and 44 Whites with genotype 1b), it is difficult to tease out the role of genotype vs. that of race. Southeast Asians with genotype 1b were five times as likely as Whites to achieve an SVR (OR, 4.63; 95% CI, 1.9–18.04), and there were no significant differences in treatment response by genotype or regimen among Southeast Asians (Dev 2002).

The duration of treatment may contribute to response rates. In San Jose, California, Nguyen and colleagues analyzed data from 38 Southeast Asians with HCV genotypes 6, 7, 8, and 9 who were treated for 24 weeks with either standard or pegylated interferon plus ribavirin. SVR was achieved by 54% (21/38), a lower rate than that reported in those with genotypes 6, 7, 8, and 9 after 48 weeks of treatment (Dev 2002; Hui 2003). There were no significant differences in response rate by treatment regimen, and the sample size was too small for analysis by genotype (M. H. Nguyen 2003).

It is not clear whether these differences reflect race, geographic diversity among Southeast Asians, genotype, a combination of these factors, or these and other additional factors. Identification of the factor(s) involved with differential responses to treatment may lead to improved treatment outcomes.

Weight

Lower body weight (≤ 85 kg /187 lbs; Fried and colleagues identified a slightly lower predictive threshold of ≤ 75 kg/165 lbs) is a known predictor of virological response to HCV treatment, whether standard or pegylated interferon is used (Fried 2002a; S. Lee 2002; Manns 2001).

Body mass index—the ratio of body weight in kilograms to the square of its height in meters—has been associated with virological and histological response to HCV treatment. Bressler and colleagues retrospectively reviewed data from 253 individuals treated with standard interferon with or without ribavirin. After controlling for age, sex, history of heavy alcohol consumption and cirrhosis at baseline, they found that a body mass index >30 kg/mg^2 was an independent predictor of virological non-response to HCV treatment (Bressler 2003). Greater body mass index also has a negative effect on histological response to treatment. In a meta-analysis of data from three HCV treatment trials, Cammá and colleagues reported that obese and overweight individuals were less likely to experience improvement of fibrosis than those with a body mass index ≤ 30 kg/mg^2 (OR, 0.56; 95% CI, 0.35–0.9) (Cammá 2004).

Weight is unique among prognostic factors, since it is the only one that may be modified by the individual. Pegylated interferon alfa-2b is dosed by body weight, as is ribavirin. It is clear that the dose of ribavirin has an impact on treatment outcomes for individuals with HCV genotype 1. The impact of ribavirin dosing on treatment outcomes has been difficult to analyze, because the dose of ribavirin has often been used as a surrogate for body weight. For individuals with HCV genotype 2 or 3, low body surface area and low body weight were the only variables significantly associated with achieving SVR (P=0.005 for low body surface areas; P=0.04 for low body weight) (Berg 2003).

Age and Sex

The likelihood of achieving a sustained virological response is greater in persons under 40 years old, and it continues to decrease with aging (Foster 2003; S. Lee 2002; Manns 2001; Poynard 1998; Poynard 2000). Females are more likely to achieve SVR than males (Manns 2001; Poynard 1998; Poynard 2000). Female sex and body weight are favorable prognostic indicators. Since females are usually smaller than men, a portion of this effect may be attributable to sex. The confluence of youth and sex appears to favor to premenopausal females, although the effect of hormones on response to treatment has not been characterized. If the favorable prognosis for treatment of young women does indeed have a hormonal component, perhaps hormones may be manipulated to increase treatment efficacy in other groups as well.

Cirrhosis

Treatment is contraindicated for individuals with decompensated cirrhosis, due to the risk of hepatic decompensation and death. Individuals with bridging fibrosis or compensated cirrhosis who have an urgent need for HCV treatment do respond to treatment, albeit less frequently than those with less advanced liver disease.

In a prospective, randomized study of standard interferon alfa-2a vs. three doses of pegylated interferon alfa-2a given to 271 individuals with bridging fibrosis or cirrhosis, the greatest virological response rate—30% SVR—was achieved with the highest dose of pegylated interferon (180 μg), although response rates for participants with poor prognostic factors (such as HCV genotype 1 and a high baseline HCV RNA level) receiving the same dose dwindled to 10%. Histological improvements occurred most frequently among those with a virological response (88% vs. 35% for non-responders) (Heathcote 2000).

Unfortunately, most data on the efficacy of pegylated interferon plus ribavirin in cirrhotics come from subgroup analyses from trials that have included only a small number of individuals with bridging fibrosis/compensated cirrhosis.

Steatosis

Hepatic steatosis—deterioration of liver tissue marked by fat deposits in liver cells—has been associated with hepatitis C infection, particularly genotype 3a, and linked with fibrosis progression (Castéra 2003; Gochee 2003; Hu 2003; Romero-Gomez 2003; Westin 2002). The presence of steatosis may decrease the probability of achieving SVR (Poynard 2003; Zeuzem 2003).

ALT and GGT Levels

High baseline alanine aminotransferase (ALT) levels and low-to-normal baseline levels of gamma-glutamyl transferase (GGT) are predictors of sustained virological response to HCV treatment (see Chapter IV, Diagnostics) (Berg 2003; S. Lee 2002; Pawlotsky 1996). Lee and colleagues, looking for baseline factors associated with achievement of an SVR, analyzed data from 814 participants in three randomized trials of pegylated interferon and found that pre-treatment ALT >3 times the upper limit of normal (ULN) was independently associated with SVR (OR=2.34; P<0.0001) (S.

Lee 2002). In an analysis of clinical, biochemical, histological, and virological characteristics of 260 participants in HCV treatment trials (of pegylated and standard interferons), a low baseline GGT level ($P<0.0001$), and a high baseline ALT level ($P=0.002$) were identified as predictors of SVR in individuals with HCV genotype 1 (Berg 2003).

Liver Histology Index

The Knodell Histological Activity Index (HAI; see Chapter IV, Diagnostics) at baseline has been identified as an independent predictor of SVR by an analysis of pooled data from three large, randomized clinical trials of pegylated interferon alfa-2a. A pre-treatment HAI score of >10 was significantly associated with SVR in cirrhotics as well as non-cirrhotics (overall, $P=0.0410$; for non-cirrhotics, $P=0.0268$) (S. Lee 2002).

Viral Kinetics

Hepatitis C viral kinetics are steady state; the continuous release of virions is balanced by a constant removal of virions from the bloodstream. The number of newly infected hepatocytes is counterbalanced by the apoptosis of infected hepatocytes. The estimated serum half-life of an HCV virion is between two and three hours (A. U. Neumann 1998). HCV-infected cells have a half-life of 1–70 days (Herrmann 2000).

Initial- and Second-Phase Viral Decay

Neumann and colleagues observed a biphasic decline in HCV by looking at blood samples from 23 HCV-infected individuals at initiation of treatment with interferon. HCV RNA levels remained at baseline for 8.7 ± 2.3 hours; then, an initial-phase decline occurred as interferon began to inhibit the production and release of new virions into the bloodstream. The amount of viral decay ranged from 0.5 to 2.0 log, depending on the dose of interferon. This decline stabilized after 24 to 48 hours of treatment. A less rapid, second-phase decline occurred between day two and day fourteen. During this second phase, interferon continued to block production of HCV, and virions were cleared from the bloodstream. The second-phase decrease in HCV-RNA is not dose-dependent (A. U. Neumann 2000).

Both the initial-phase rapid decline and the slower, second-phase decline in HCV RNA levels may be predictors of response to treatment. Although the second-phase decline has been regarded as the best predictor of SVR, the initial phase decline (at 24 hours after initiation of treatment) may be an important predictor of second-phase decline and, therefore, an early predictor of response to treatment (Carlsson 2002; Jessner 2001; Layden 2002a; Layden 2002b). A retrospective analysis of two studies by Layden and colleagues found strong correlations with lower viral loads at the end of the 24-hour initial-phase decline and more rapid second-phase declines ($P<0.001$). Individuals with HCV RNA <250,000 copies/mL after the first phase of viral decay were the only ones who achieved sustained virological responses (Layden 2002a). In another study of the predictive value of HCV RNA levels 24 hours after initiation of treatment, Jessner and colleagues observed that individuals with viral load decreases of less than 70% of baseline were likely to be non-responders after 24 weeks of treatment. This would mean that an individual with a baseline viral load of 2,000,000 copies/mL would most likely be a non-responder if his or her viral load remained above

600,000 copies/mL 24 hours after initiating treatment. This approach identified non-responders with a specificity of 100%, a sensitivity of 83%, a positive predictive value of 100%, and a negative predictive value of 77% (Jessner 2001).

More evidence to support the predictive value of 24-hour viral loads comes from Ferenci and colleagues, who observed that those with 12-week EVRs experienced sharper declines in 24-hour viral loads than non-responders. In week-12 responders, 24-hour viral load declines were 1.19 log ± 0.43 (SD), while non-responders had 24-hour viral load declines of 0.55 log ± 0.36 (SD) (Ferenci 2002).

Hopefully, research will identify individuals who are likely to have virological, biochemical, and histological responses early in the course of treatment. Until more information about predictors of biochemical and histological responses in the absence of virological responses is available, treatment decisions based on a 24-hour viral load must be considered premature. Some individuals may see much-needed improvements in liver histology even in the absence of virological response; discontinuing treatment would prevent an opportunity for histological benefit.

Early Stopping Rules

The likelihood of achieving sustained virological response to treatment may be predicted by early virological response after 12 weeks of treatment. Individuals who do not have either an undetectable HCV RNA or a 2-log decrease in HCV RNA are unlikely to have an SVR (Davis 2003b; Castro 2002; Civeira 1999; Fried 2002a; S. Lee 2002; A. U. Neumann 1998; Rosen 2002). Fried and colleagues found that 65% (253/390) of those treated with pegylated interferon alfa-2a plus ribavirin who achieved EVR also achieved SVR. Only 3% (2/63) of the individuals without an EVR had an SVR (Fried 2002a).

In a meta-analysis of data from trials of pegylated interferon alfa-2a, Lee and colleagues found a negative predictive value (NPV) of EVR of 91% at week 4; it increased slightly to 95% at week 8, and rose to 98% at week 12 (a high NPV is used to determine when therapy can be discontinued, because achieving an SVR after completing the full course of treatment is extremely unlikely). The positive predictive value (PPV) of an EVR, according to this meta-analysis, was not as useful for guiding treatment decisions (the higher the PPV, the more likely that an individual may achieve an SVR; a high PPV may encourage people to continue treatment). At week 4, the positive predictive value of EVR was 54%; it decreased to 49% at week 8 and to 46% at week 12 (S. Lee 2002).

Data from an earlier study by McHutchison and colleagues, which used standard interferon (either with or without ribavirin), revealed that detectable HCV RNA at 12 weeks of therapy predicted non-response in 89% of individuals; waiting until 24 weeks to identify non-responders (by detectable HCV RNA) increased this to 99% (McHutchison 2001). It is possible, however, that the regimen of standard interferon used in this study may have influenced the length of time necessary for identifying non-responders. Using a 24 week cutoff for non-response derived from a standard interferon treatment trial may not be applicable to persons treated with pegylated interferon.

In an effort to develop an algorithm for early discontinuation of HCV treatment applicable to both standard and pegylated interferon-based regimens, Berg and colleagues analyzed data from 209 individuals enrolled in five different HCV treatment protocols. Pre-treatment virological, histological,

biochemical, and clinical parameters were examined for their importance in predicting SVR. Participants received 24 or 48 weeks of treatment. Treatment included ribavirin (dose of 800 –1,200 mg/day), with the exception of 19 individuals who received pegylated interferon alfa-2a monotherapy. Regimens included two different induction/maintenance strategies with standard interferon alfa-2a, thrice weekly standard interferon (alfa-2a and alfa-2b), and two pegylated interferon-based regimens—alfa-2b (Peg-Intron®) and alfa-2a (Pegasys®). HCV RNA testing was performed on stored serum samples at baseline and after 4 and 12 weeks of treatment.

The predictive thresholds for baseline HCV RNA, baseline ALT and baseline GGT levels, and HCV RNA levels at week 4 and week 12 were identified; week 12 cutoff values were used for the algorithm. At week 12, the NPV of HCV RNA ≤ 30,000 IU/mL was 100%; positive predictive value was 64.8%. There were no significant differences in the applicability of these thresholds by treatment regimen.

The algorithm proposed by Berg and colleagues recommends discontinuation of treatment at week 12 if HCV RNA is >30,000 IU/mL, or if there has been less than a 2-log (99%) decrease in HCV RNA from baseline. If HCV RNA is between 30,000 and 35,000 IU/mL, repeat testing is recommended. For those with HCV RNA below the threshold of discontinuation, a qualitative HCV RNA test should be performed at 24 weeks; if HCV RNA is detectable at that time, the algorithm recommends discontinuation of treatment (Berg 2003).

Additional research using viral kinetics to determine early stopping rules is underway. Using data from 127 participants treated with 180 μg/week of pegylated interferon alfa-2a plus 1,000–1,200 mg/day of ribavirin for 48 weeks, Neumann and colleagues worked to identify the earliest reliable time point and decrease in HCV RNA level for predicting sustained virological response. No one achieved an SVR unless their HCV RNA was <5.5 log on treatment day four, or they had a decrease of >0.5 log (approximately a threefold drop) on treatment day seven. These parameters had a negative predictive value of 100% (A. U. Neumann 2003). Prospective studies are needed to validate these and other early stopping rules.

Duration of Treatment

Extending HCV treatment for an additional 24 weeks has been suggested as a strategy to improve treatment outcomes in genotype 1. Drusano and colleagues developed a model to predict SVR after treatment with pegylated interferon alfa-2b, using data from participants in the Manns trial. The model predicted that individuals with genotype 1 would need to have continuously undetectable HCV RNA for at least 32 weeks to achieve a sustained virological response. Since the model found that, on average, it took 30.2 weeks for HCV RNA to become undetectable, the authors suggested that 48 weeks of treatment might be insufficient for genotype 1 (Drusano 2004). Although this model has limits, a prospective investigation could help to identify individuals who might benefit from extended therapy.

However, extending duration of therapy may increase treatment discontinuations rather than sustained virological response rates. Sanchez-Tapias randomized 326 individuals who had detectable HCV RNA after 4 weeks of treatment to either 44 or 68 additional weeks of pegylated interferon alfa-2a plus 800 mg/day of ribavirin, for a total of 48 or 72 weeks of treatment. Although they did not observe an increase in neutropenia or thrombocytopenia with longer

treatment, they reported a difference in withdrawal rates by treatment duration (17% vs. 36% in the extended duration group). Sustained virological response rates did not differ significantly by treatment arm (30% for 48 weeks vs. 36% for 72 weeks) (Sanchez-Tapias 2004). The rate of sustained virological responses was not broken out by genotype in this study, so it is difficult to assess the effect of extended treatment on virological responses in genotype 1.

Conversely, a subset of individuals with genotype 2 or genotype 3 may achieve sustained virological responses after less than 24 weeks of treatment. In a randomized, prospective study of 280 individuals with genotype 2 and 3, Mangia and colleagues used HCV RNA level after 4 weeks of treatment to determine duration of treatment for 210/280 individuals; the remaining 70 were treated for 48 weeks. When HCV RNA was undetectable at 4 weeks, treatment was discontinued at 12 weeks. Those with detectable HCV RNA at week 4 were treated for a total of 24 weeks. SVR was achieved more frequently among those treated for 12 weeks than 24 or 48 weeks (89.9%, 78.7% and 81.4%, respectively). Relapse rates were lowest after 48 weeks of treatment; they increased from 0-2.5% after 24 weeks of treatment and 10% after 12 weeks of treatment (Mangia). Response rates were greater among those with genotype 2 (82%) than those with genotype 3 (64%), regardless of duration of treatment. This study used a lower dose of pegylated interferon alfa-2b (1.0 μg/kg per week) and a higher dose of ribavirin (1,000–1,200 mg/day) than has been recommended for treatment of genotype 2 and genotype 3 (P-IFN 1.5 μg/kg per week; RBV 800 mg/day). Prospective study of early virological responses with different doses of pegylated interferon and ribavirin will help to clarify optimal regimen and duration of therapy for persons with genotype 2 and genotype 3.

The Difficulty of Comparison

Although study results from trials of each drug have been compared (often by one company or the other, to indicate its product's advantage), there has not been a head-to-head comparison of the safety, efficacy, and tolerability of the two pegylated interferons. Efficacy, safety, and tolerability of each product appear similar, but without a direct comparison we must rely on the experience of clinicians who have used both products. While it is tempting to compare the two, a true comparison is not possible; participant characteristics and treatment regimens differ across studies. The only comparison to date is a small study of hepatitis C viral kinetics during treatment with Pegasys® or Peg-Intron® and ribavirin. A suboptimal dose of Peg-Intron® was used in this study (1.0 μg/kg, the recommended dose for Peg-Intron® monotherapy; 1.5 μg/kg is the recommended dose for combination therapy). The study compared mean week-12 viral loads, finding that those who received Pegasys® had significantly lower viral loads (2.82 $\log_{10}$ vs. 3.87 $\log_{10}$; $P<0.01$) (Bruno 2002). This information raises questions about the recommended dose for Peg-Intron® monotherapy.

Key Studies of Combination Therapy: Pegylated Interferon Plus Ribavirin

Three pivotal large, randomized clinical trials of pegylated interferon plus ribavirin (with similar inclusion/exclusion criteria) have shown that the combination of pegylated interferon plus ribavirin is the most effective treatment for chronic hepatitis C. Overall sustained virological response rates are often presented as evidence of treatment efficacy in all individuals with chronic hepatitis C although individuals with one or more poor prognostic factors were excluded from these trials.

The Manns Data

Manns and colleagues conducted a large (1,530 person), three-arm study, comparing the safety and efficacy of:

- Standard interferon alfa-2b (3 MIU, thrice weekly), plus ribavirin dosed at 1,000–1,200 mg/day for 48 weeks;
- Pegylated interferon alfa-2b (1.5 μg/kg, once weekly), plus ribavirin dosed at 800 mg/day for 48 weeks; and
- Pegylated interferon alfa-2b (1.5 μg/kg, once weekly for four weeks, then reduced to 0.5 μg/kg), plus ribavirin dosed at 1,000–1,200 mg/day for 48 weeks.

Comparisons across treatment arms are problematic in the Manns study. It is possible that the induction/maintenance arm did not offer its participants a sufficient dose of pegylated interferon, while those in the higher-dose pegylated interferon arm may not have received a sufficient dose of ribavirin. It's as if someone tried to bake three cakes: one with a proper proportion of known ingredients (but using inferior flour), one with not quite enough baking powder, another with not quite enough flour—and then looked to see if the cakes rose nonetheless.

Figure 3. Sustained Virological Responses by Treatment Regimen

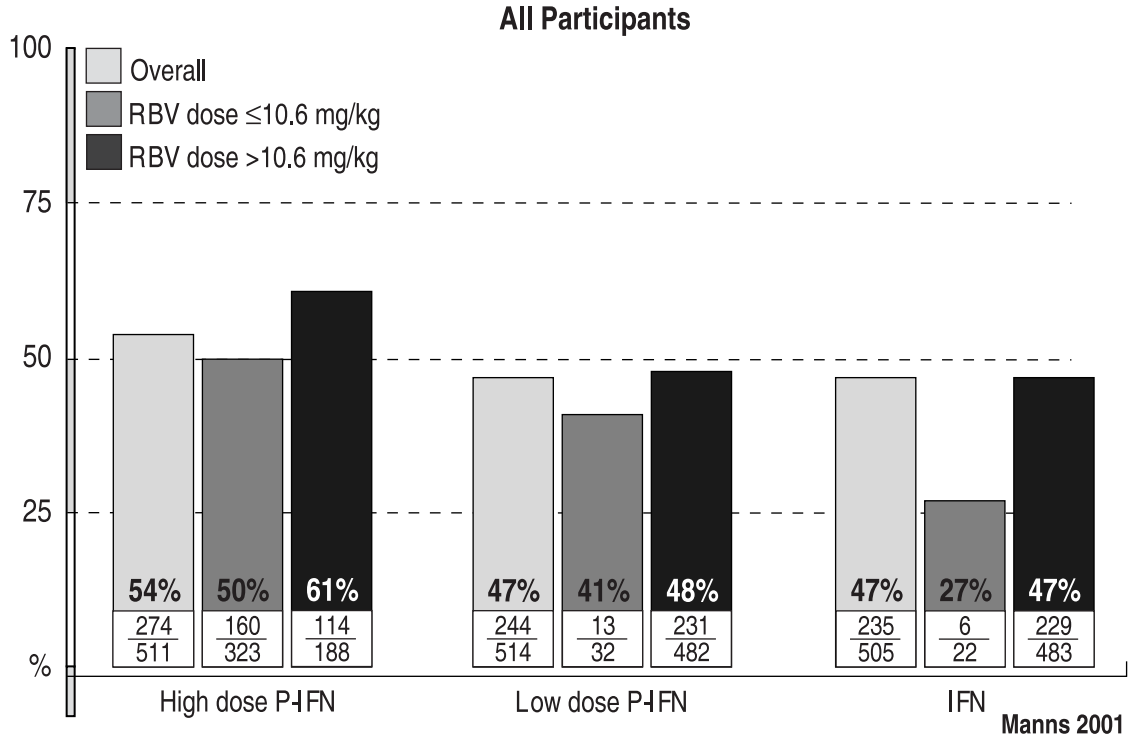
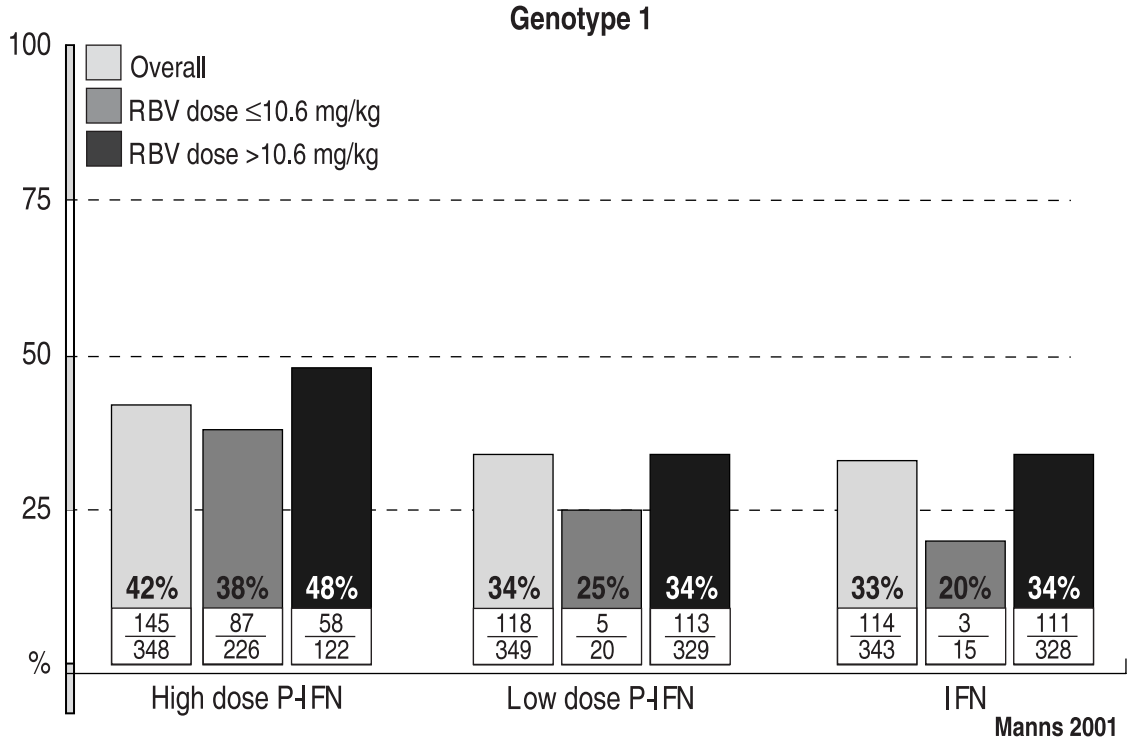


Figure 4. Sustained Virological Response by Genotype



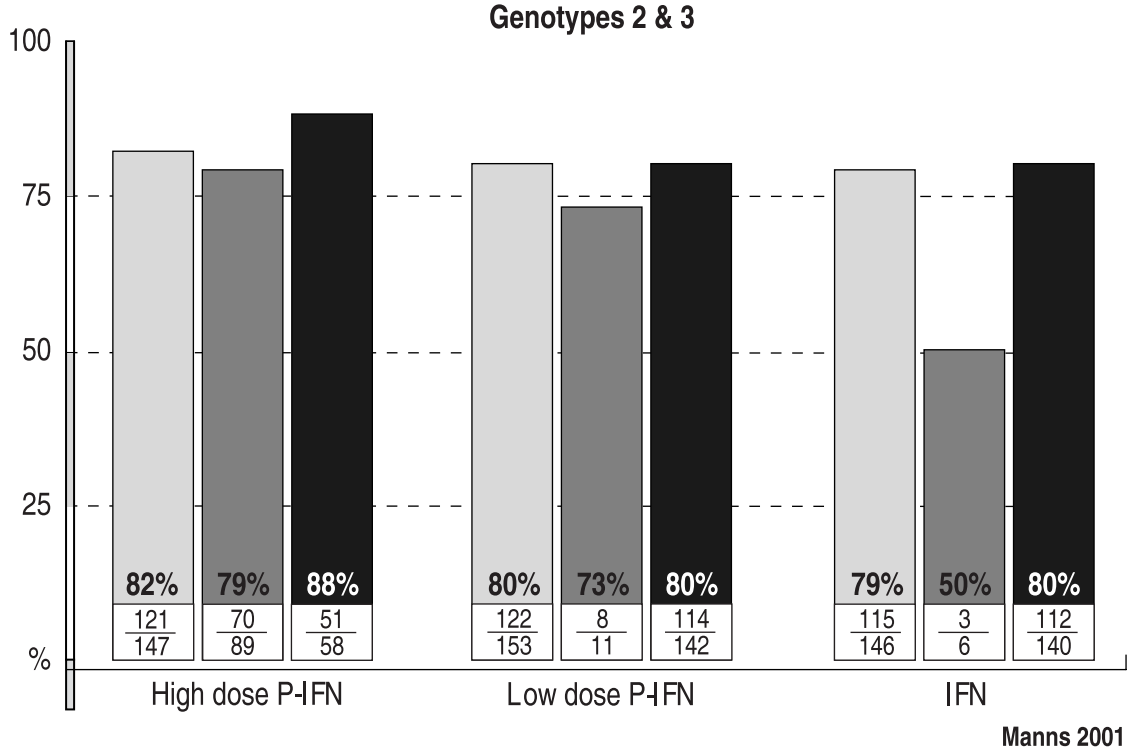
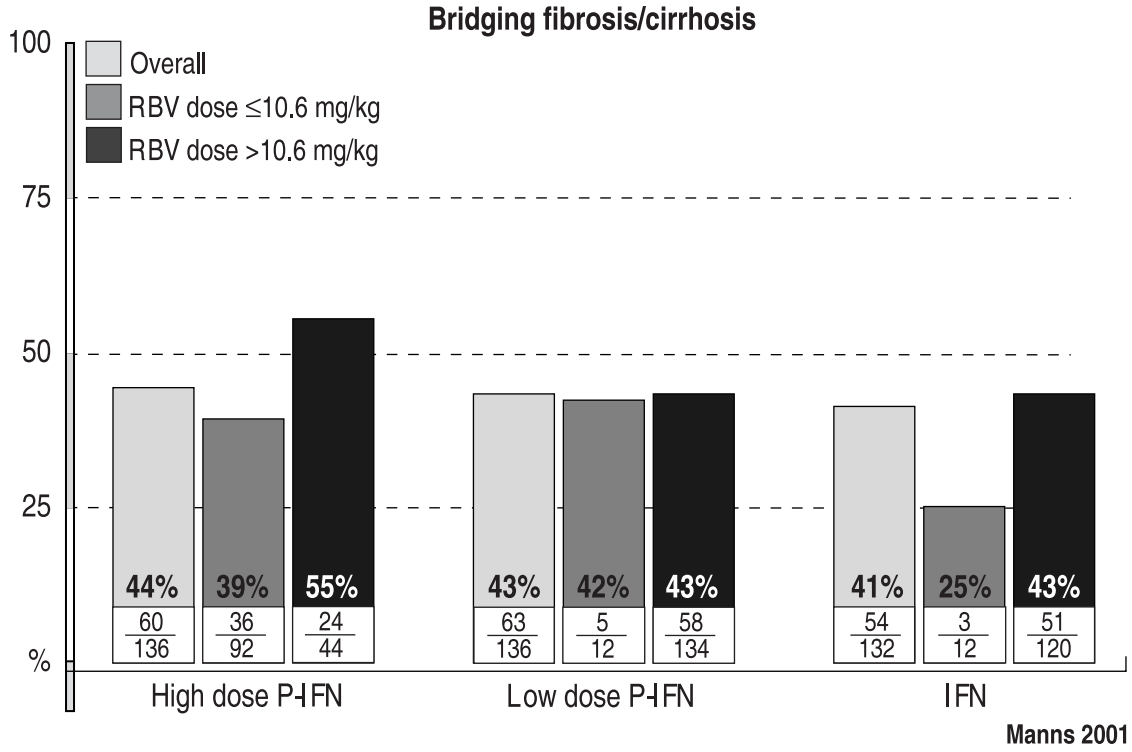
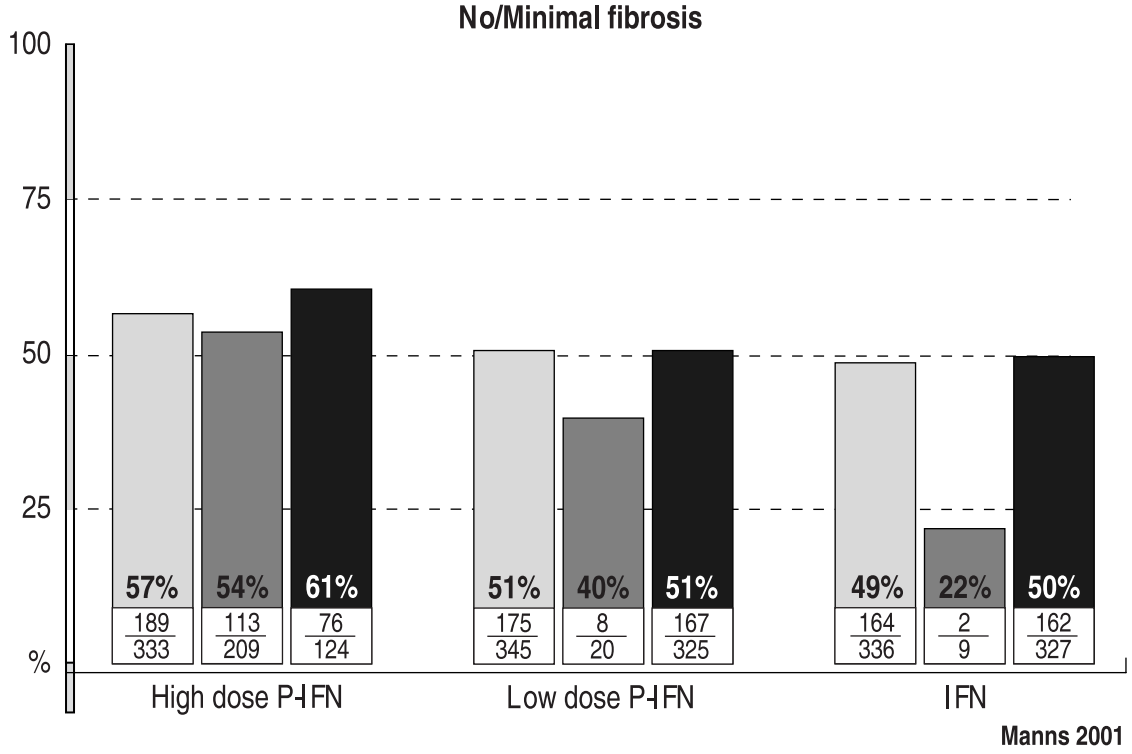


Figure 5. Sustained Virological Response by Liver Histology



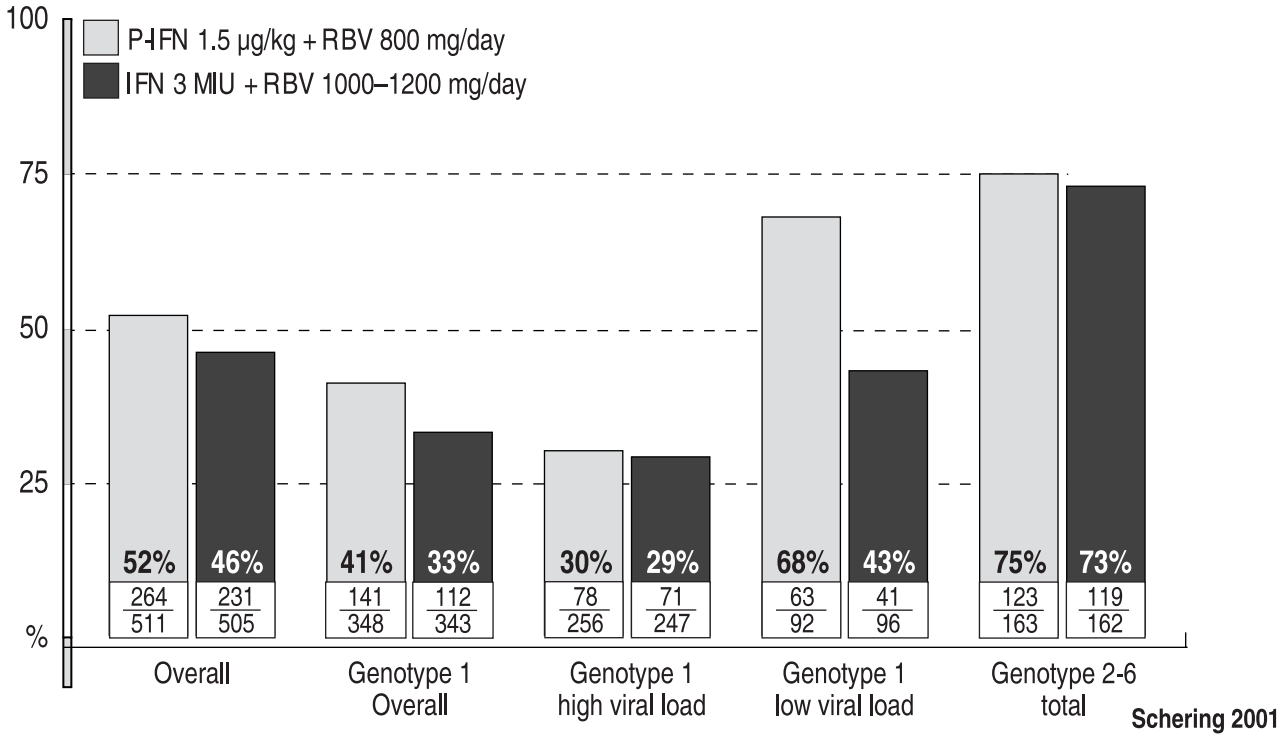


The probability of achieving an SVR increased with the higher doses of ribavirin and pegylated interferon (OR, 1.7; P=0.002). When weight-based dosing of ribavirin was taken into account, the estimated effect of high-dose (vs. lower dose) pegylated interferon was larger (OR, 1.7); however, post hoc analysis used ribavirin dose as a proxy for, rather than a reflection of, body weight. (Weight-based dosing of ribavirin has been correlated with greater response rates in many studies of RBV plus standard or pegylated interferon.) Unfortunately, these data led to the approval of Peg-Intron® with a recommended daily dose of 800 mg of ribavirin, which may be suboptimal for some individuals. Higher doses of ribavirin are recommended in the European Union (1,000 mg daily for individuals who weigh less than 75 kg (165 lbs) and 1,200 mg daily for individuals who weigh 75 kg or more), but statistically significant prospective data on the efficacy of weight-based ribavirin are not yet available.

Overall, SVR occurred most frequently with the higher dose of pegylated interferon (54% vs. 47% for the other two dosing arms). In the same higher dose arm, 42% of those with genotype 1 and 42% of those with a high baseline viral load (>2 million) achieved SVR.

Possessing genotype 1 and a high baseline viral load substantially influenced the response to treatment. When response rates are broken out by baseline viral load and genotype, significant differences by baseline viral load among those with genotype 1 emerge. Only 30% of those with a high baseline viral load achieved SVR after treatment with pegylated interferon 1.5 μg/kg plus 800 mg of RBV, while 68% with low baseline viral loads achieved SVR. Among those with genotype 1/high baseline viral load, there was virtually no difference in response by regimen (30% for P-IFN vs. 29% for standard IFN). While the package insert includes this data, the study did not include this analysis, which is relevant for the majority of people in the United States contemplating HCV treatment.

Figure 6. Response by Genotype, Baseline HCV RNA Level, and Treatment Regimen



The Manns study did not address questions about the optimal duration of therapy for each HCV genotype. All participants received 48 weeks of therapy, which may have been longer than necessary for those with genotype 2 or genotype 3. A year before the Manns study was published, Poynard and colleagues, based on their analysis of data from 1,744 treatment-naïve persons in two large trials, suggested discontinuation of treatment (standard interferon plus ribavirin) for individuals with HCV genotype 2 or genotype 3 who had undetectable HCV RNA after completing 24 weeks of therapy. They found that 82% of those with HCV genotype 2 or genotype 3 who were HCV-RNA-undetectable after 24 weeks of therapy achieved SVR. If therapy was continued for an additional 24 weeks, the rate of SVR rose by only 2% (Poynard 2000). A look at the Manns data broken out by genotypes 2 and 3 shows very little difference by treatment regimen. It is difficult to tell whether the similarities in response between the lower-dose pegylated interferon arm and the standard interferon arm are a consequence of an insufficient dose of pegylated interferon, differing baseline HCV RNA levels within genotypes, or other prognostic factors.

Figure 7. Sustained Virological Response Rate by Treatment Regimen and Genotype

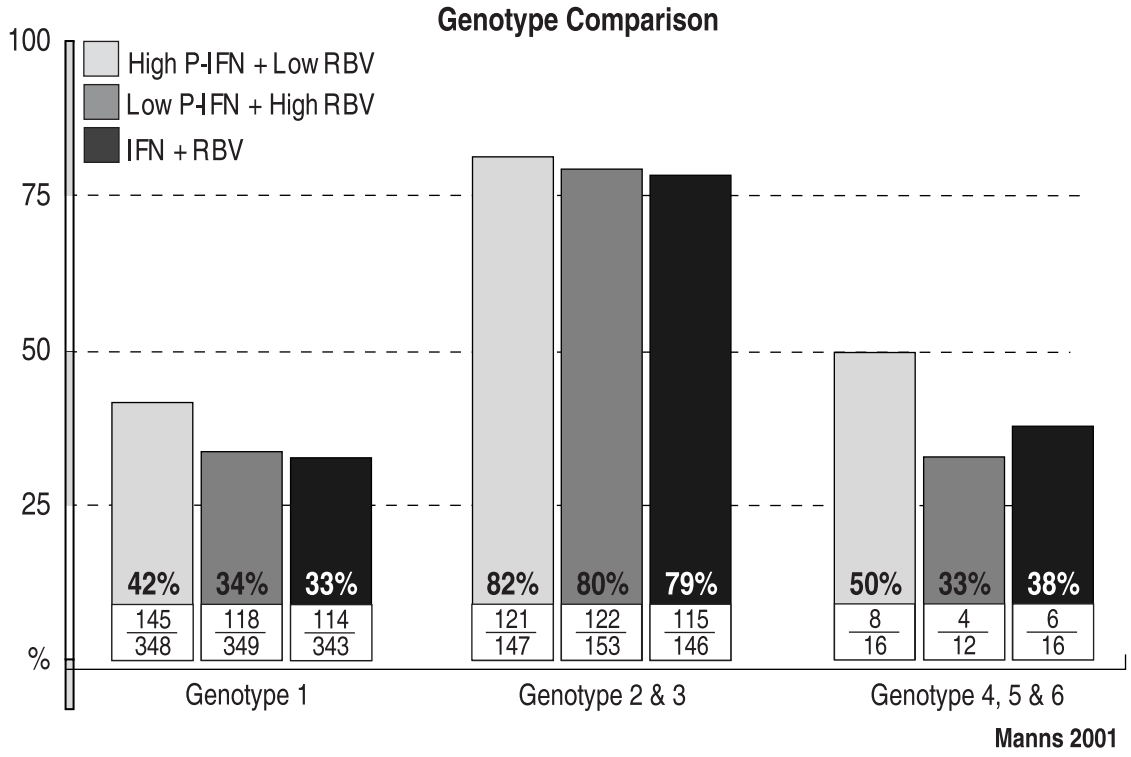
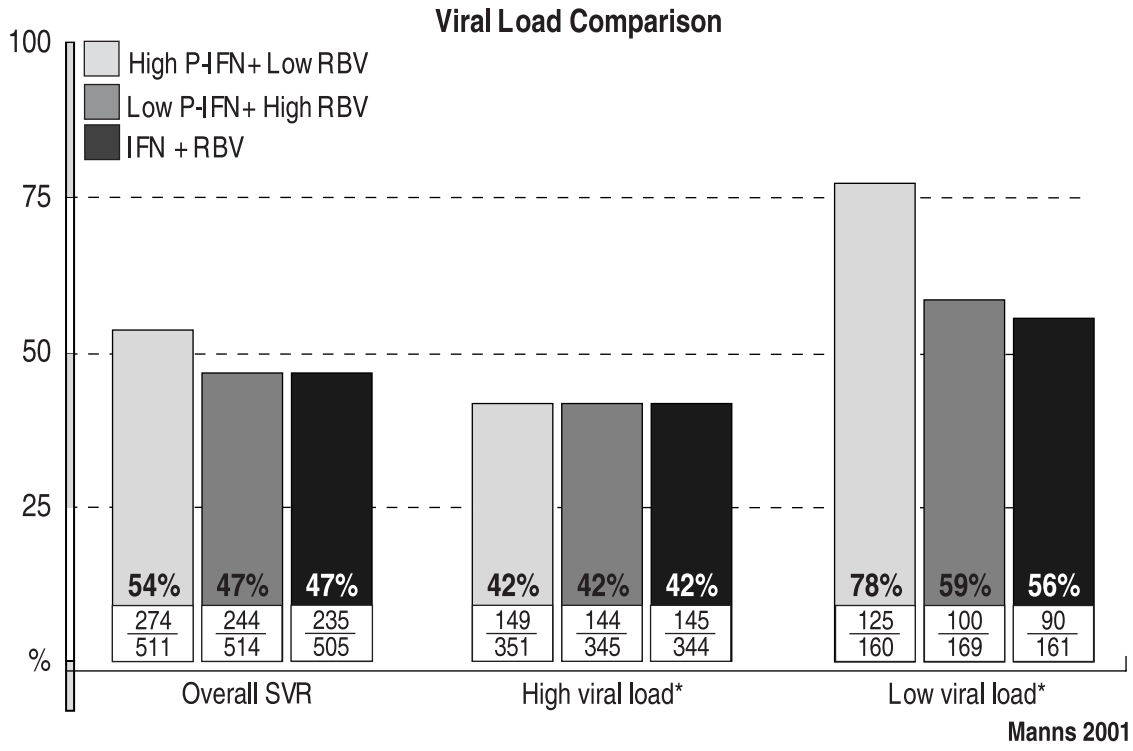
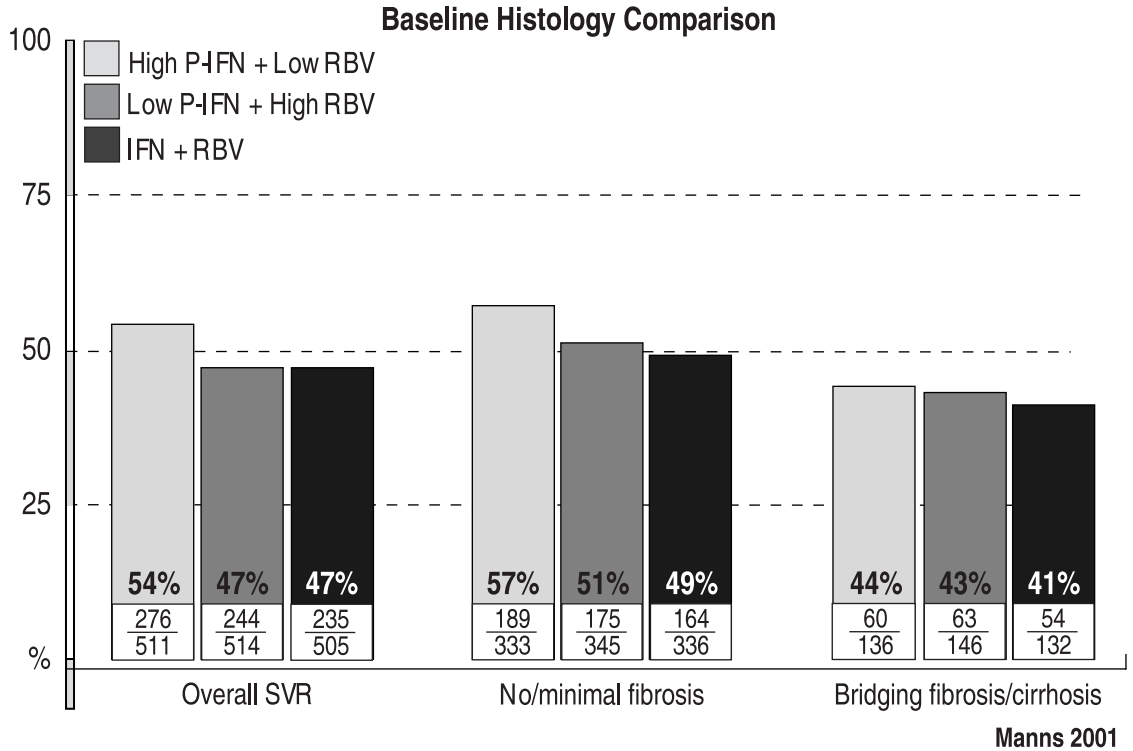


Figure 8. Sustained Virological Response Rate by Treatment Regimen and Baseline Viral Load



* High viral titer, >2 million; low viral titer, ≤ 2 million

Figure 9. Sustained Virological Response Rate by Treatment Regimen and Liver Histology



Although many did not achieve a sustained virological response, histological improvement was observed in all treatment groups. Histological improvement occurred most frequently with SVR; 90% of those who achieved an SVR also had improvement in liver histology. Some degree of histological improvement (ranging from -0.8 to -1.3) was seen in 44% of non-responders. About 20% of each treatment group had improvement of fibrosis (defined as a decrease of at least one in the Knodell HAI score). However, without long-term follow up, it is not possible to assess the durability and clinical impact of such improvements in relapsers and non-responders.

Dose reductions due to neutropenia occurred in 18% of those on high-dose pegylated interferon vs. 8% on standard interferon. Only 1% discontinued treatment because of neutropenia. Dose modifications were more frequent with pegylated interferon/high-dose ribavirin than with standard interferon/high-dose ribavirin arm (49% vs. 34%), mostly due to neutropenia.

Table 2. Treatment Discontinuations and Dose Reductions for Adverse Events

Adverse Events	High dose P-IFN/ Low dose RBV	Low dose P-IFN/ High dose RBV	IFN/ High dose RBV
Asthenia (weakness)	18 % (92/511)	16% (82/514)	18% (91/505)
Fatigue	64% (327/511)	62% (318/514)	60% (303/505)
Fever	46% (235/511)	44% (226/514)	33% (167/505)
Headache	62% (316/511)	58% (298/514)	58% (293/505)
Rigors (stiffness and/or chills)	48% (245/511)	45% (231/514)	41% (207/505)
Weight decrease	29% (148/511)	17% (87/514)	20% (101/505)
Dizziness	21% (107/511)	21% (108/514)	17% (86/505)
Arthralgia (joint pain)	34% (174/511)	34% (175/514)	28% (141/505)
Musculoskeletal pain	21% (107/511)	17% (87/514)	19% (96/505)
Myalgia (muscle pain)	56% (286/511)	48% (247/514)	50% (252/505)
Anorexia	32% (163/511)	29% (149/514)	27% (136/505)
Diarrhea	22% (112/511)	16% (82/514)	17% ((86/505)
Nausea	43% (220/511)	36% (185/514)	33% (167/505)
Vomiting	14% (71/511)	14% (72/514)	12% (61/505)
Impaired concentration	17% (87/511)	16% (82/514)	21% (106/505)
Depression	31% (158/511)	29% (149/514)	34% (172/505)
Insomnia	40% (204/511)	40% (206/514)	41% (207/505)
Irritability	35% (179/511)	34% (175/514)	34% (172/505)
Coughing	17% (87/511)	15% (77/514)	13% (66/505)
Dyspnea (difficulty breathing)	26% (133/511)	23% (118/514)	24% (121/505)
Alopecia (hair thinning or loss)	36% (184/511)	29% (149/514)	32% (162/505)
Pruritus (itching)	29% (149/511)	26% (134/514)	28% (141/505)
Rash	24% (123/511)	22% (113/514)	23% (116/505)
Dry skin	24% (123/511)	18% (93/514)	23% (116/505)
Injection site inflammation	25% (128/511)	27% (139/514)	18% (91/505)
Injection site reaction	58% (296/511)	59% (303/514)	36% (182/505)

Manns 2001

Adverse events were clustered in five groups: flulike symptoms, gastrointestinal symptoms, psychiatric symptoms, respiratory symptoms, and dermatological symptoms. The adverse events reported in this chart occurred in at least 10% of study participants. The number of individuals experiencing more than one adverse event was not provided.

Table 3. Adverse Events By Treatment Regimen

Adverse Events	High dose P-IFN/ Low dose RBV	Low dose P-IFN/ High dose RBV	IFN/ High dose RBV
Dose discontinuation for any adverse event	14% (71/511)	13% (67/514)	13% (65/503)
Dose reduction for any adverse event	42% (214/511)	36% (185/514)	34% (171/503)
for anemia	9% (46/511)	12% (62/514)	13% (65/503)
for neutropenia	18% (92/511)	10% (51/514)	8% (40/503)

Manns 2001

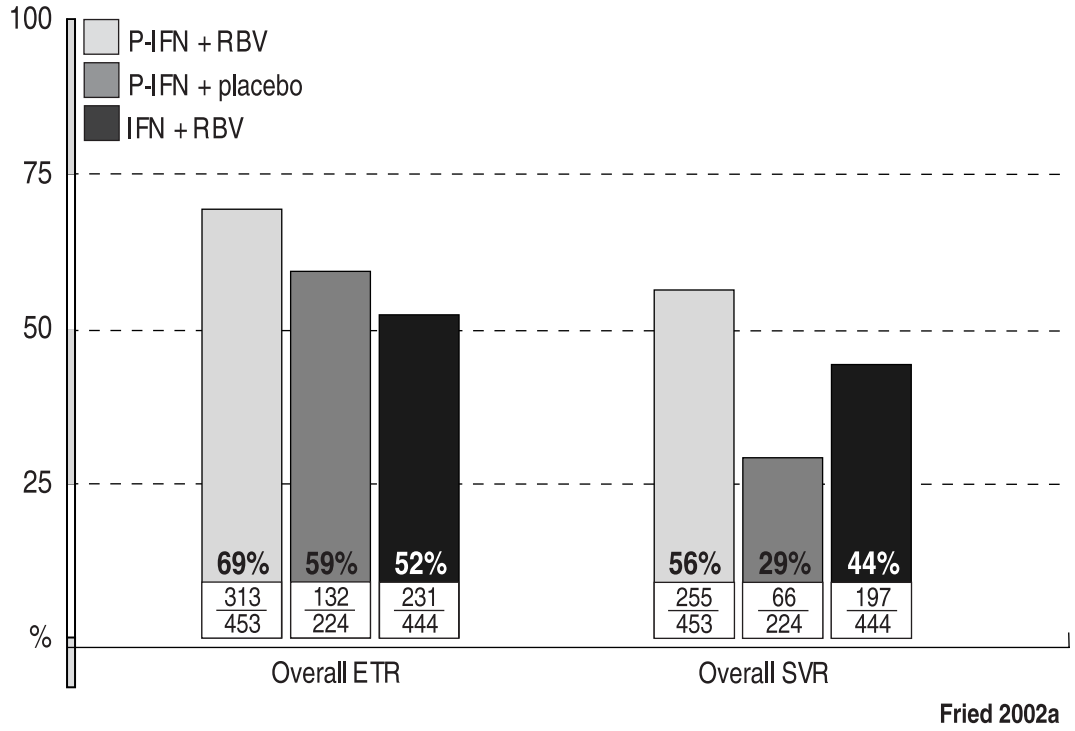
Discontinuation rates were similar across arms (13% from the pegylated interferon arm and 14% from the standard interferon arm).

The Fried Data

Fried and colleagues conducted a large, international trial, in which 1,121 individuals with chronic HCV were randomized into one of three treatment arms:

- Pegylated interferon alfa-2a ,180 μg once weekly, plus ribavirin 1,000–1,200 mg/day for 48 weeks;
- Pegylated interferon alfa-2a, 180 μg once weekly, plus placebo for 48 weeks; or
- Standard interferon alfa-2b, 3 MIU thrice weekly, plus ribavirin 1,000–1,200 mg/day for 48 weeks.

Figure 10. End-of-Treatment and Sustained Virological Responses by Regimen



The label of Copegus® (Roche's ribavirin) breaks out SVR data by genotype.

Figure 11. Sustained Virological Responses by Regimen and Genotype

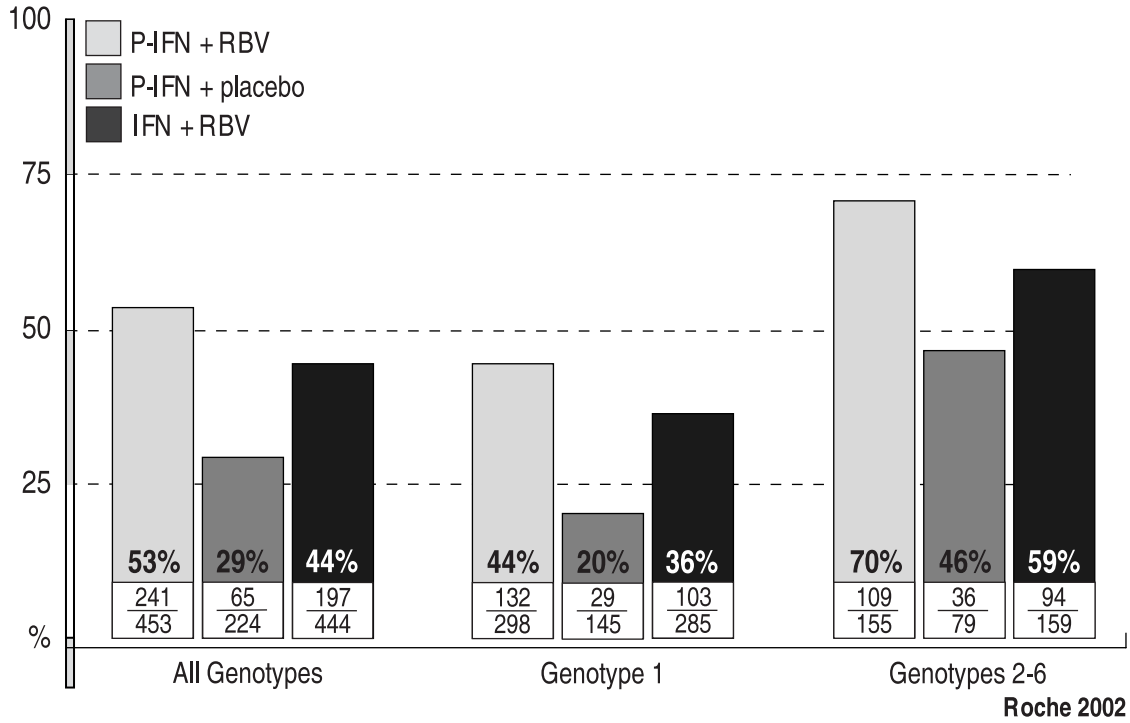


Figure 12. Sustained Virological Response Rate by Regimen and Genotype: High Baseline HCV RNA

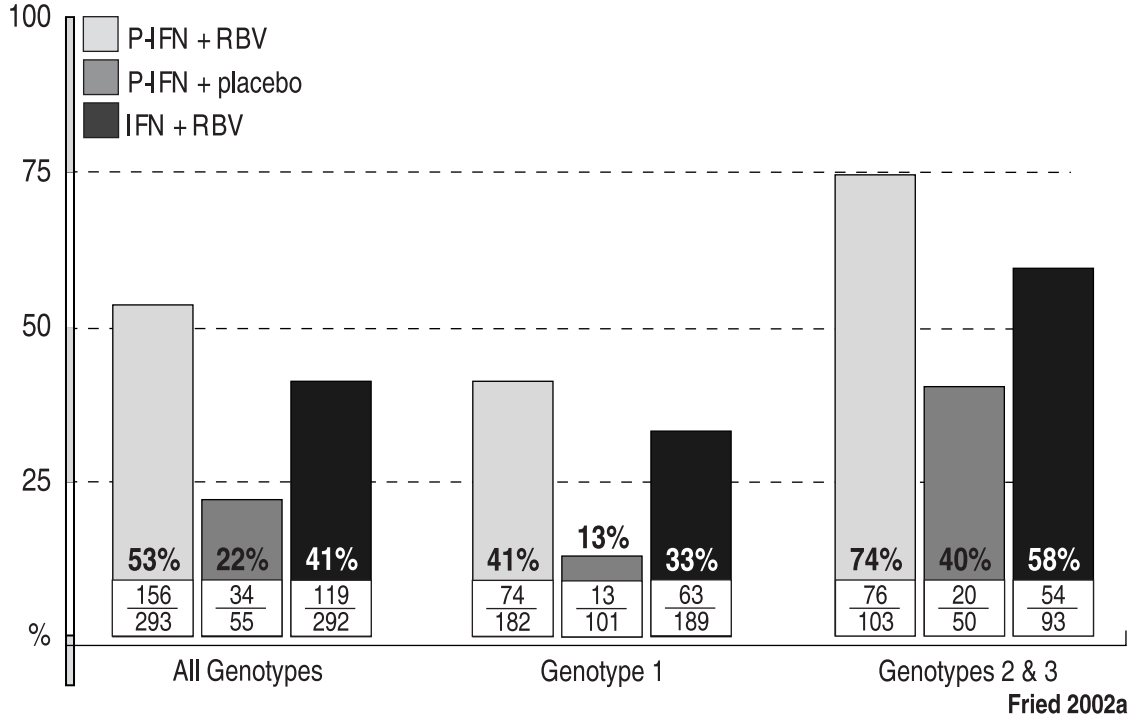


Figure 13. Sustained Virological Response Rate by Regimen and Genotype: Low Baseline HCV RNA

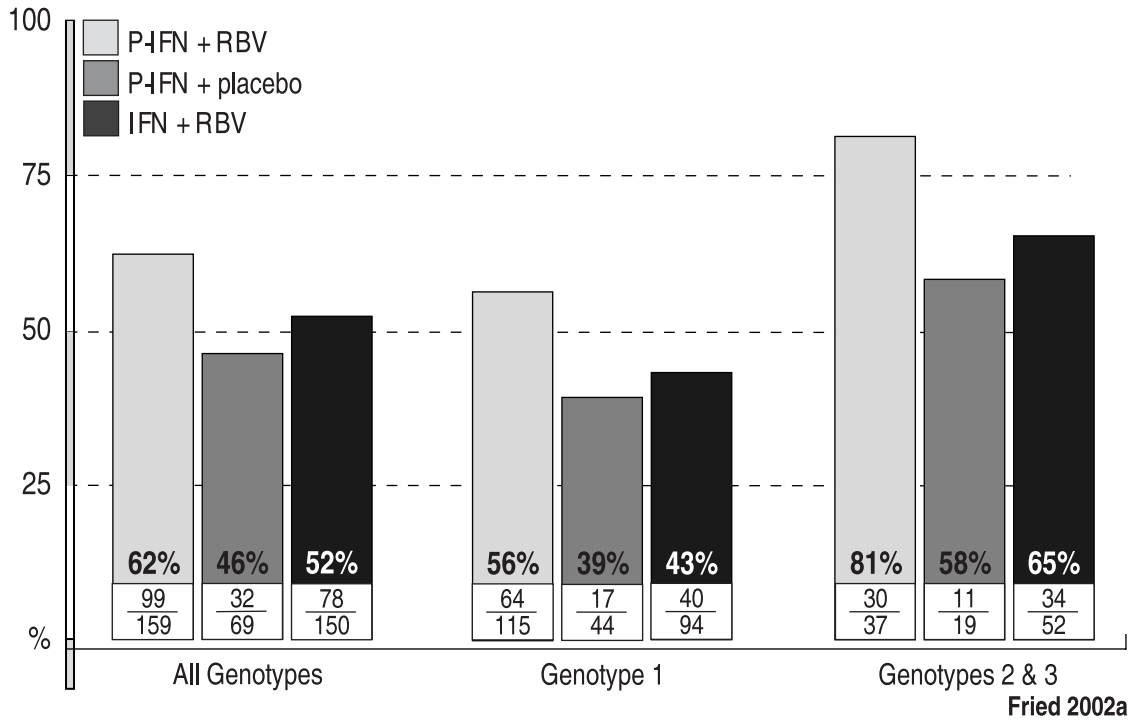
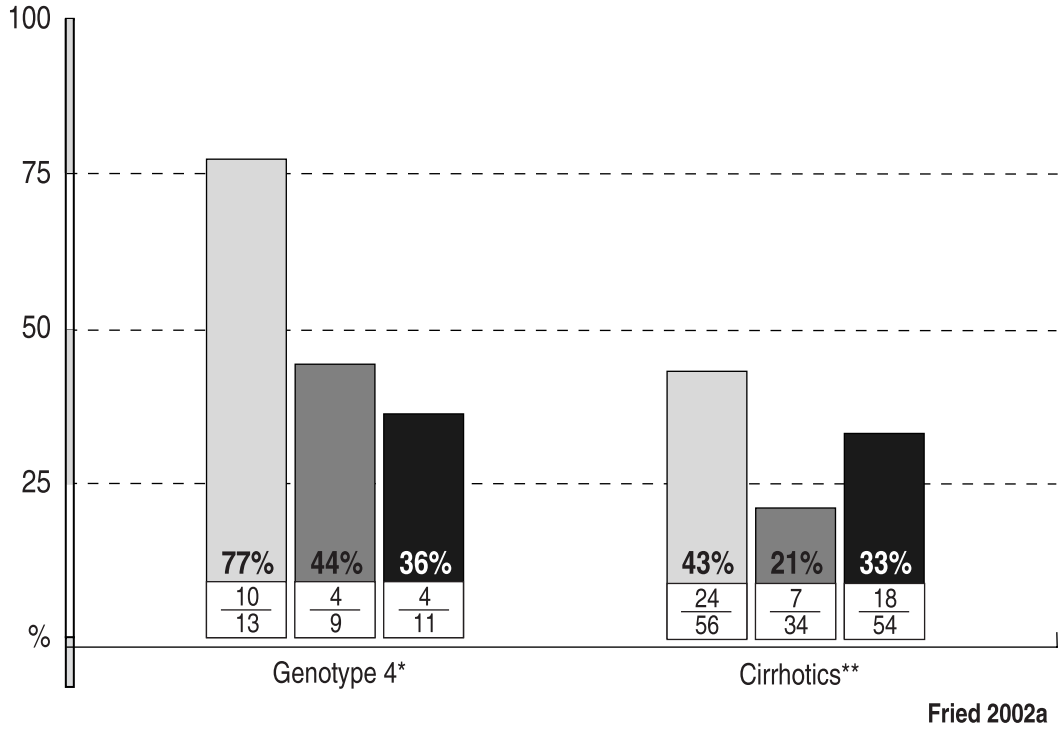


Figure 14. Sustained Virological Response Rate: Genotype 4 and Cirrhosis



* Data not broken out by baseline viral load.
** Data not broken out by baseline viral load or genotype.

Duration of therapy by genotype was not addressed in this study, nor were questions about optimal dosing of pegylated interferon and ribavirin, although interesting information emerged about SVR and dose modifications. The rate of SVR among individuals with early virological responses in the P-IFN/RBV arm was 75%. When the authors looked at early virological responders from the same arm that had significant dose reductions (of at least 20% in doses of both drugs), the rate of SVR only dropped to 67%. Further exploration of the safety and efficacy of lower doses of pegylated interferon alfa-2a (150 μg or 135 μg) is needed.

Aside from a greater frequency of neutropenia and thrombocytopenia, adverse events from the pegylated interferon arm were similar to those in the standard interferon arm. People on pegylated interferon had fewer flulike symptoms and less frequent depression than those on standard interferon.

Table 4. Dose Modifications Due to Laboratory Abnormalities*

Lab Abnormalities	P-IFN + RBV		IFN + RBV		P-IFN + Placebo	
Anemia	1% (4/453)	22% (99/453)	3% (13/444)	19% (83/444)	0% (0/224)	4% (8-224)
Neutropenia	20% (91/453)	1% (6/453)	5% (24/444)	<1% (1/444)	17% (38/224)	0% (0/224)
Thrombocytopenia	4% (18/453)	<1% (2/453)	<1% (1/444)	0% (0/453)	6% (14/224)	<1% (1/224)

Fried 2002a

*Laboratory abnormalities also included elevations of alanine aminotransferase levels (not shown).

Table 5. Discontinuations for Laboratory Abnormalities and Adverse Events

Discontinuations	P-IFN + RBV	IFN + RBV	P-IFN + Placebo
Overall	22% (100/453)	32% (140/444)	32% (72/224)
For lab abnormalities	3% (12/453)	1% (4/444)	1% (2/224)
For adverse events	7% (32/453)	10% (44/444)	6% (13/224)

Fried 2002a

There were three deaths in this trial (due to hypertensive heart disease, drowning, and liver cancer), none considered to be related to treatment.

The Haziyannis Data

Hadziyannis and colleagues took a closer look at ribavirin dosing and duration of therapy by genotype in a multinational, randomized, four-arm study of 1,284 individuals with chronic hepatitis C. Participants received a fixed dose of pegylated interferon alfa-2a (180 μg once weekly) for either 24 or 48 weeks, with ribavirin doses of either 800mg/day or 1,000–1,200 mg/day. The four arms of the study were:

- Arm one: pegylated interferon alfa-2a, 180 μg once weekly, plus 800 mg/day of ribavirin for 24 weeks;
- Arm two: pegylated interferon alfa-2a, 180 μg once weekly, plus 1,000–1,200 mg/day of ribavirin for 24 weeks;
- Arm three: pegylated interferon alfa-2a, 180 μg once weekly, plus 800 mg/day of ribavirin for 48 weeks; and
- Arm four: pegylated interferon alfa-2a, 180 μg once weekly, plus 1,000–1,200 mg/day of ribavirin for 48 weeks.

Randomization was stratified by genotype and viral titer (low vs. high: below or at least 2 million copies). Individuals with genotype 1/high viral load were randomized 1 to 1 to 4 to 4 (10%, 10%, 40%, 40%). Individuals with a non-1 genotype and a low viral titer were randomized 1 to 1.5 to 1 to 1.5 (20%, 30%, 20%, 30%). Due to this randomization scheme, the results of this trial are comparable only within a particular genotype and viral load stratum; the overall virological response across arms does not reflect a purely random distribution of baseline characteristics.

Table 6. Randomization and Allocation

	24-week		48-week	
Genotype & Viral Load	P-IFN + RBV 800	P-IFN + RBV 1000–1200	P-IFN + RBV 800	P-IFN + RBV 1000–1200
Genotype 1 & high VL	1 (10%)	1 (10%)	4 (40%)	4 (40%)
Genotype 1 & low VL	1 (20%)	1.5 (30%)	1 (20%)	1.5 (30%)
Genotype non-1 & high VL	1 (20%)	1.5 (30%)	1 (20%)	1.5 (30%)
Genotype non-1 & low VL	1 (20%)	1.5 (30%)	1 (20%)	1.5 (30%)

FDA 2002

Table 7. Baseline Characteristics

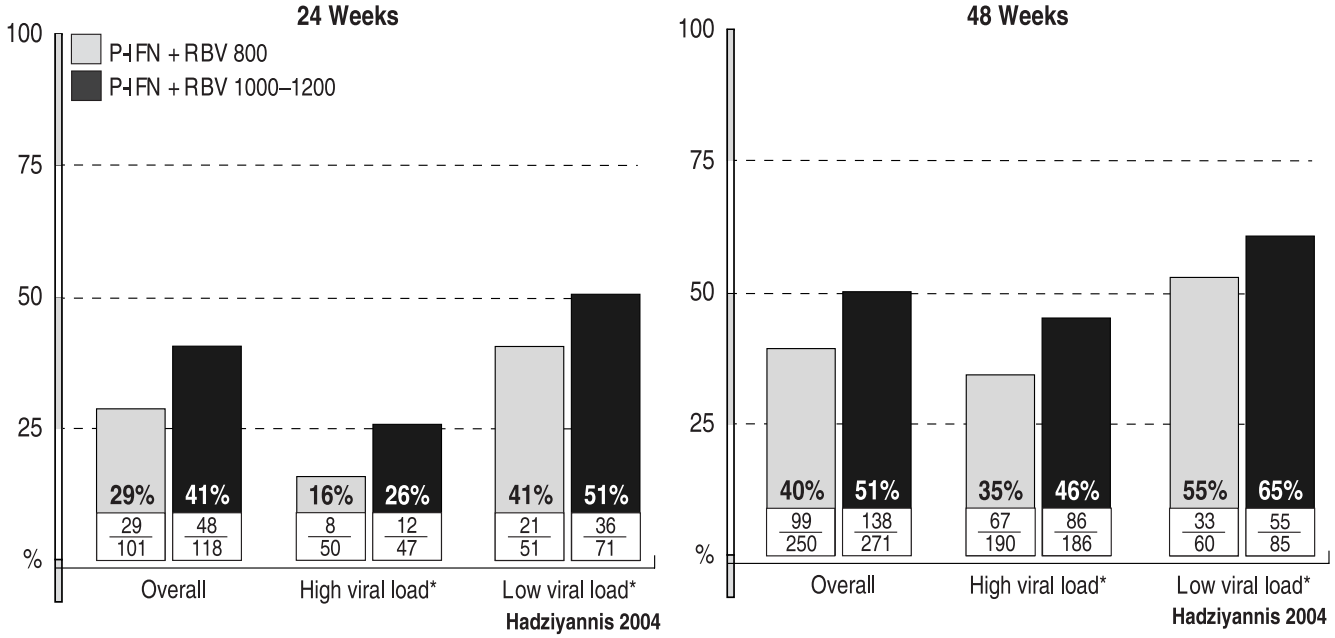
Characteristics	Total (N=1284)	U.S. (N=441)	Non-U.S. (N=843)
High viral load	64 % (819)	65% (288)	63 % (531)
Genotype 1	58% (740)	61% (270)	56% (843)
Cirrhosis	25% (321)	29% (127)	23% (194)

FDA 2002

Data were analyzed by modified intention-to-treat, including everyone who received at least one dose of medication (1284/1311), rather than everyone who was enrolled. Individuals who did not achieve a week-24 virological response were offered the option of treatment discontinuation.

Most participants were white males (65% male; 89% white). Roche is sponsoring another trial (the National Institutes of Health's Study of Viral Resistance to Anti-Viral Therapy [Virahep-C]) that will evaluate response to treatment among African Americans. Unfortunately, the number of African Americans with genotype non-1 infections enrolled in this trial was too small to draw any conclusions about dosing, duration, and the likelihood of achieving SVR in this group.

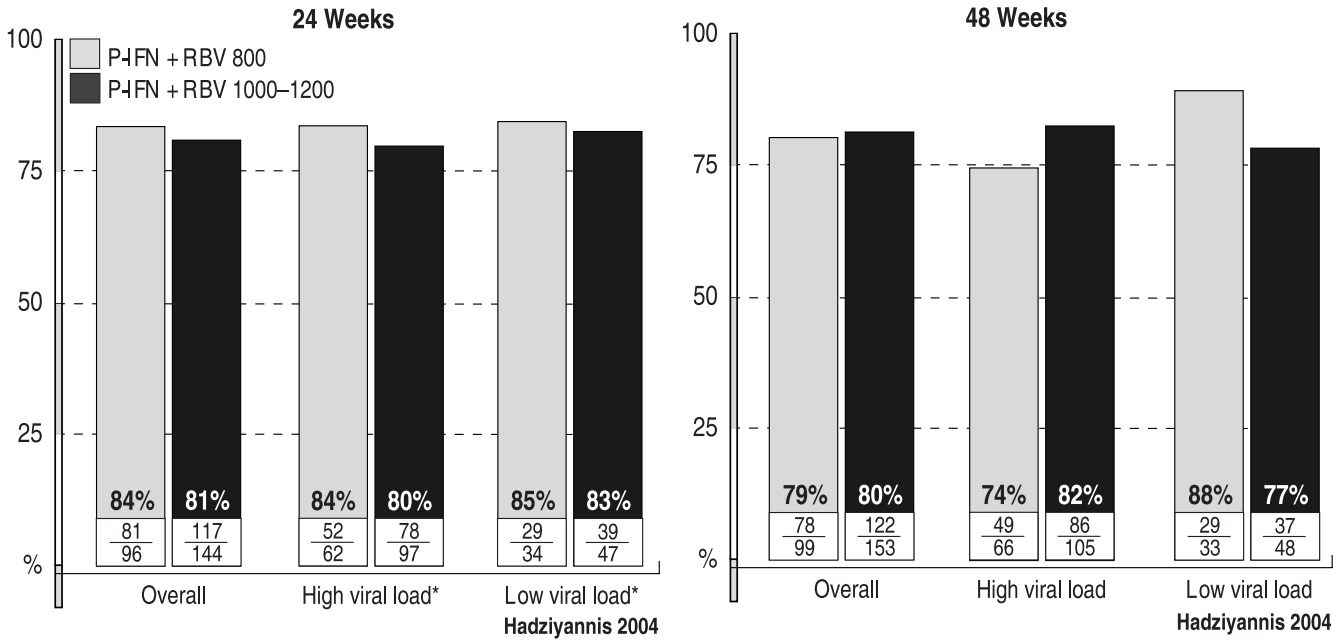
Figure 15. Sustained Virological Response Rate in Genotype 1 by Regimen, Treatment Duration, and Baseline Viral Load



* High viral titer is >2 million copies; low viral titer is ≤ 2 million copies.

The Hadziyannis data is especially relevant to most people in the United States, where genotype 1 is predominant. Forty-eight weeks of treatment with weight-based dosing of ribavirin yielded the highest rate of sustained virological responses for individuals with genotype 1, regardless of baseline viral load.

Figure 16. Sustained Virological Response Rate in Genotypes 2 and 3 by Regimen, Treatment Duration, and Baseline Viral Load



Response rates for HCV genotypes 2 and 3 did not differ significantly by regimen or duration of treatment . For people with genotype-2 and genotype-3 infections, 24 weeks of treatment and a lower ribavirin dose appear to be as effective as a 48-week course of treatment and a higher ribavirin dose. There were fewer severe adverse events and discontinuations among those who received 24 weeks of therapy with the lower dose of ribavirin. This is good news for people with HCV genotypes 2 and 3.

Figure 17. Sustained Virological Response Rate in Genotype 1 by Regimen, Treatment Duration, and Baseline Liver Histology

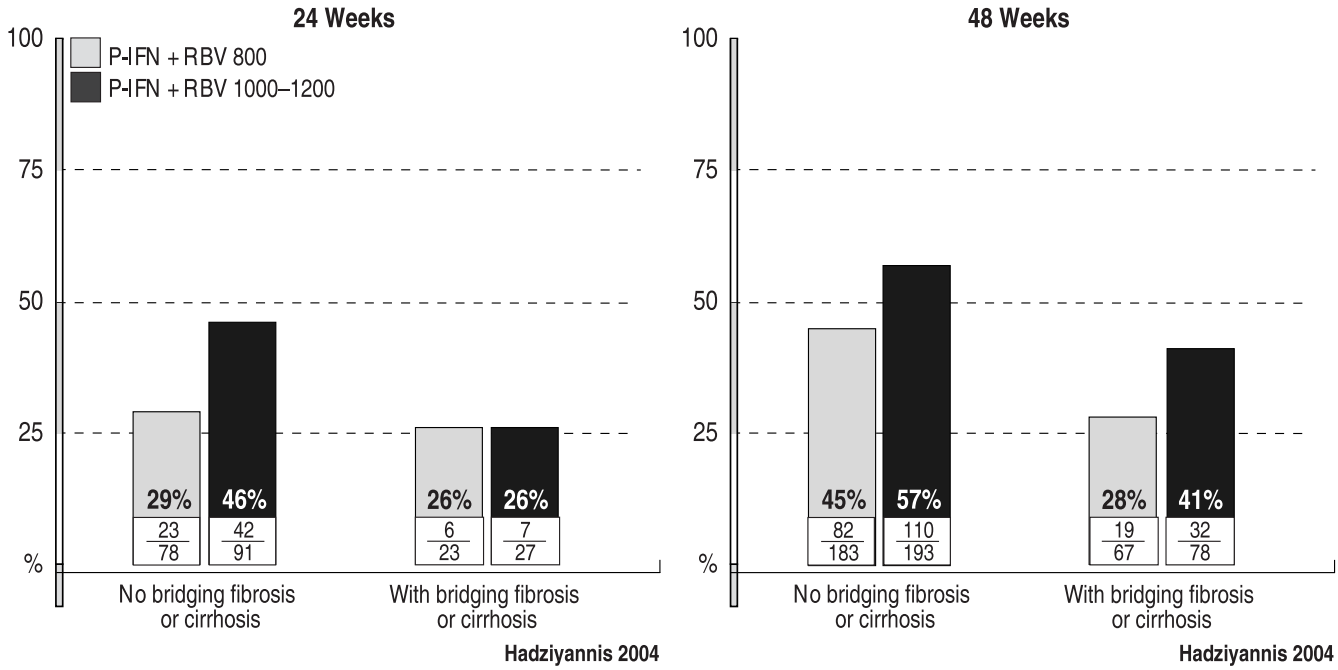
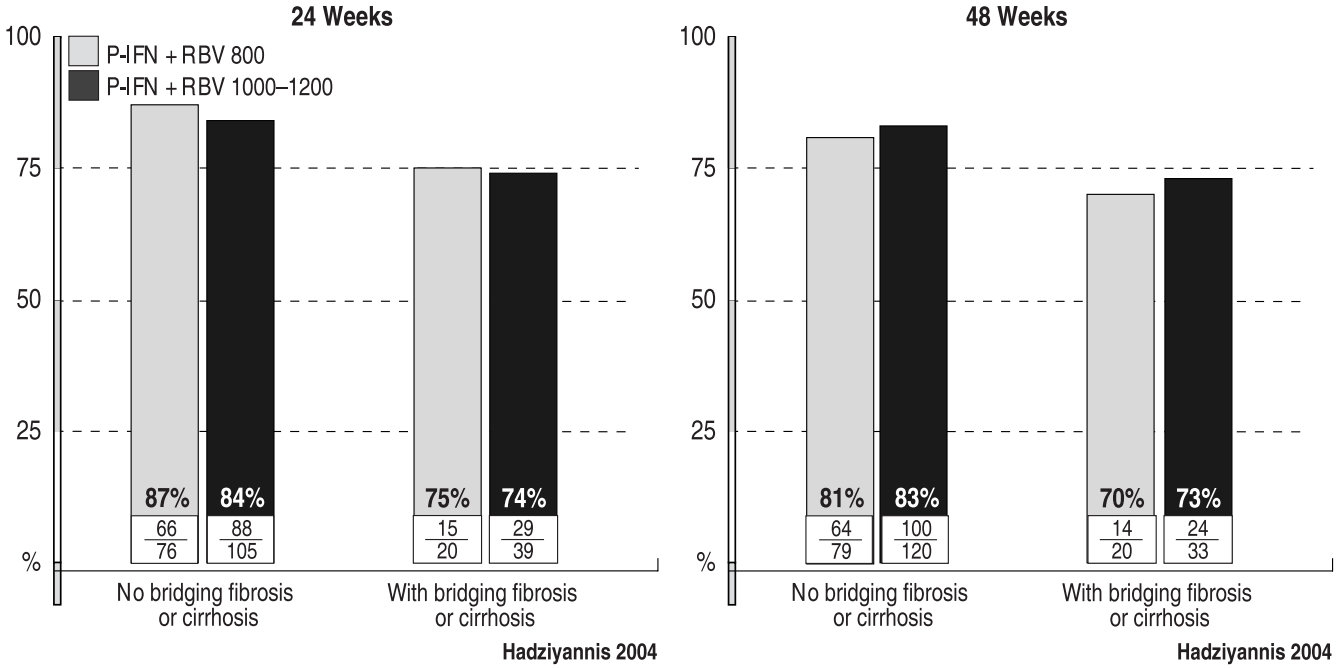


Figure 18. Sustained Virological Response Rate in Genotype 2 and 3 by Regimen, Treatment Duration, and Baseline Liver Histology



Here, HCV genotype remains a significant prognostic factor among individuals with bridging fibrosis or cirrhosis, although the sample size was small. Among those with genotype 2 or 3 and serious liver damage, neither duration of treatment nor dose of ribavirin had a significant impact on SVR. In genotype 1, the highest rate of SVR was achieved with both the greater duration of treatment and the higher of ribavirin. Unfortunately, no data on changes in liver histology were available.

Other interesting information emerged about treatment response and toxicities based on geographic region. There were 441 participants in the U.S. and 843 non-U.S. participants (from Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Mexico, the Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Taiwan, and the UK). Participants in the U.S. experienced more treatment-related toxicities and achieved SVR less frequently than did non-U.S. participants (FDA 2002).

Table 8. Prognostic Factors in U.S. and Non-U.S. Participants

Characteristics	U.S. Participants	Non-U.S.
HCV genotype 1	61%	56%
> 44 years of age	52%	33%
Body weight > 85 kg	47%	22%
Cirrhosis	29%	23%

FDA 2002

The difference in response rates may be attributed in part to a greater proportion of poor prognostic factors among U.S. participants. However, HCV genotype 1 in the U. S. may be a different entity than non-U.S. genotype 1, since there can be substantial genetic diversity among strains within a genotype (see Chapter IV, Diagnostics). It is possible that genotype 1 infections in the U.S. may

respond differently to treatment than genotype 1 infections in other parts of the world.

This study did not resolve questions about optimal dosing of pegylated interferon. Initially, a fixed dose of pegylated interferon was given to all participants. Treatment-related hematologic abnormalities were managed by dose modification rather than through administration of hematopoietic growth factors. Overall, more than 30% of those receiving 48 weeks of therapy modified or omitted at least one dose of pegylated interferon.

Table 9. Pegylated Interferon and Ribavirin Dose Modifications by Study Arm

	24-week		48-week	
Dose Modification	**P-IFN + RBV $_{800}$**	**P-IFN + RBV $_{1000–1200}$**	**P-IFN + RBV $_{800}$**	**P-IFN + RBV $_{1000–1200}$**
RBV	19% (39/207)	27% (76/280)	28% (101/361)	38% (166/436)
P-IFN	30% (63/207)	26% (73/280)	33% (120/361)	36% (159/436)

Hadziyannis 2004

Adverse events reported by 20% of those who received at least one dose of study medications, from most to least common, included flulike symptoms, insomnia, irritability, hair loss, itching, depression and skin inflammation.

Table 10. Severe and Serious Adverse Events (SAEs)

	24-week		48-week	
Adverse Events	**P-IFN + RBV $_{800}$**	**P-IFN + RBV $_{1000–1200}$**	**P-IFN + RBV $_{800}$**	**P-IFN + RBV $_{1000–1200}$**
Overall severe events	22% (46/207)	23% (63/280)	32% (116/361)	32% (141/436)
Overall serious events	3% (7/207)	7% (19/280)	9% (33/361)	10% (44/436)
Treatment-related serious events	1% (3/307)	3% (8/280)	4% (15/361)	3% (14/436)
Deaths*	0	1 (<1%)	1 (<1%)	2 (<1%)

Hadziyannis 2004

* Two deaths were unrelated to therapy (both drug overdoses). Of the two therapy-related deaths, one was caused by septicemia associated with neutropenia, and one by suicide.

Table 11. Treatment Withdrawals By Study Arm

	24-week		48-week	
Treatment Withdrawl	**P-IFN + RBV $_{800}$**	**P-IFN + RBV $_{1000–1200}$**	**P-IFN + RBV $_{800}$**	**P-IFN + RBV $_{1000–1200}$**
For any reason	7% (14/207)	8% (22/280)	32% (117/361)	27% (117/436)
For AE & lab abnormality	5% (10/207)	5% (13/280)	16% (59/361)	15% (67/436)
For insufficient response	0 (<1%)	0 (<1%)	9% (31/361)	6% (24/436)

Hadziyannis 2004

Pegylated Interferon Monotherapy

Although combination therapy with ribavirin is considered to be the current standard of care for the treatment of chronic hepatitis C, ribavirin may be contraindicated for some individuals who still need to treat their HCV. Ribavirin has caused birth defects and death in exposed animal fetuses at doses as low as one-twentieth of those recommended for human beings. Consequently, it is contraindicated for men and women who are planning a pregnancy; pregnant women and their sexual partners; and breast-feeding women.

For those engaging in procreative sex, the use of two forms of contraception during treatment and for six months after completion of treatment is recommended. Ribavirin is contraindicated for persons with severe renal impairment (creatinine clearance of <50 mL/min); individuals with a history of significant or unstable cardiac disease; individuals with hemoglobinopathies (e.g., sickle-cell anemia, thalassemia major); autoimmune hepatitis; advanced hepatic decompensation (before or during treatment); and anyone allergic to ribavirin.

Little is known about the safety and efficacy of ribavirin in transplant recipients and individuals with HIV/HBV/HCV infection. More data are needed on safety and efficacy of ribavirin in persons under 18 years of age. Roche's pediatric safety and efficacy study of Pegasys® with and without Copegus® is expected to open in mid-2004; final data will not be available for several years. Schering has not performed pharmacokinetic evaluations of ribavirin in this population. Little is known about the response to ribavirin in geriatric individuals, as there have been so few study participants over 65 years of age, nor have there been pharmacokinetic evaluations of ribavirin in the elderly. Clearly, data concerning safety, efficacy and pharmacokinetics are needed in these populations.

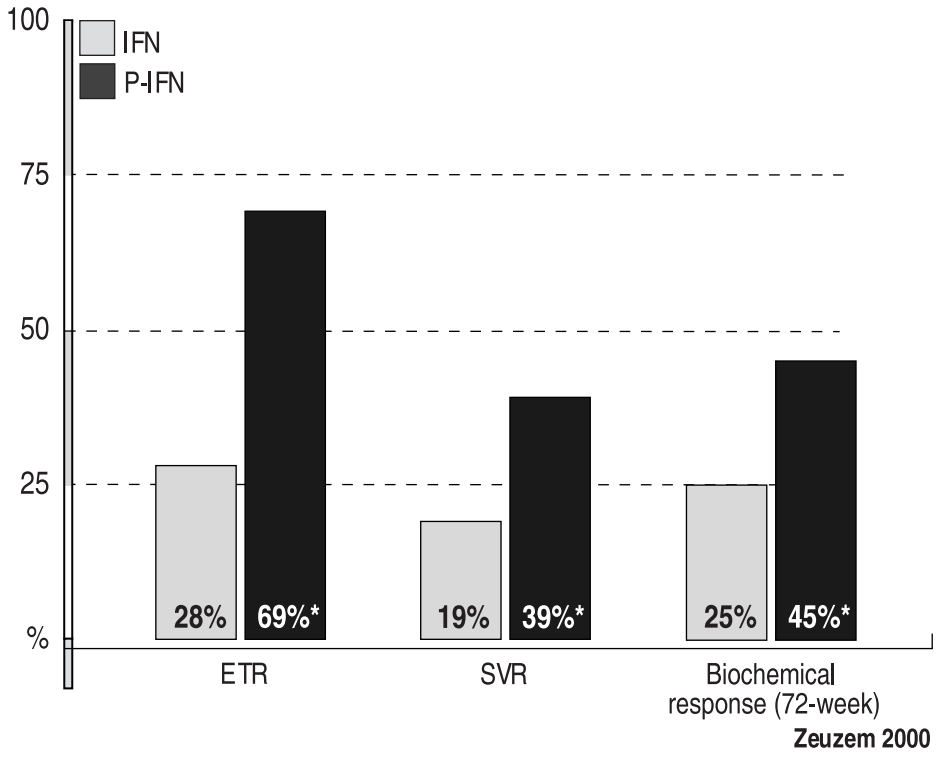
Results from two large randomized, controlled trials of treatment-naïve individuals established the efficacy of pegylated interferon monotherapy is superior to that of standard interferon monotherapy (Lindsay 2001; Zeuzem 2000). These studies provide a wealth of data on the dosing, efficacy, side effects and adverse events of pegylated interferon therapy.

The Zeuzem Data

Zeuzem and colleagues compared pegylated interferon monotherapy to standard interferon monotherapy in a study of 531 individuals randomized to receive either:

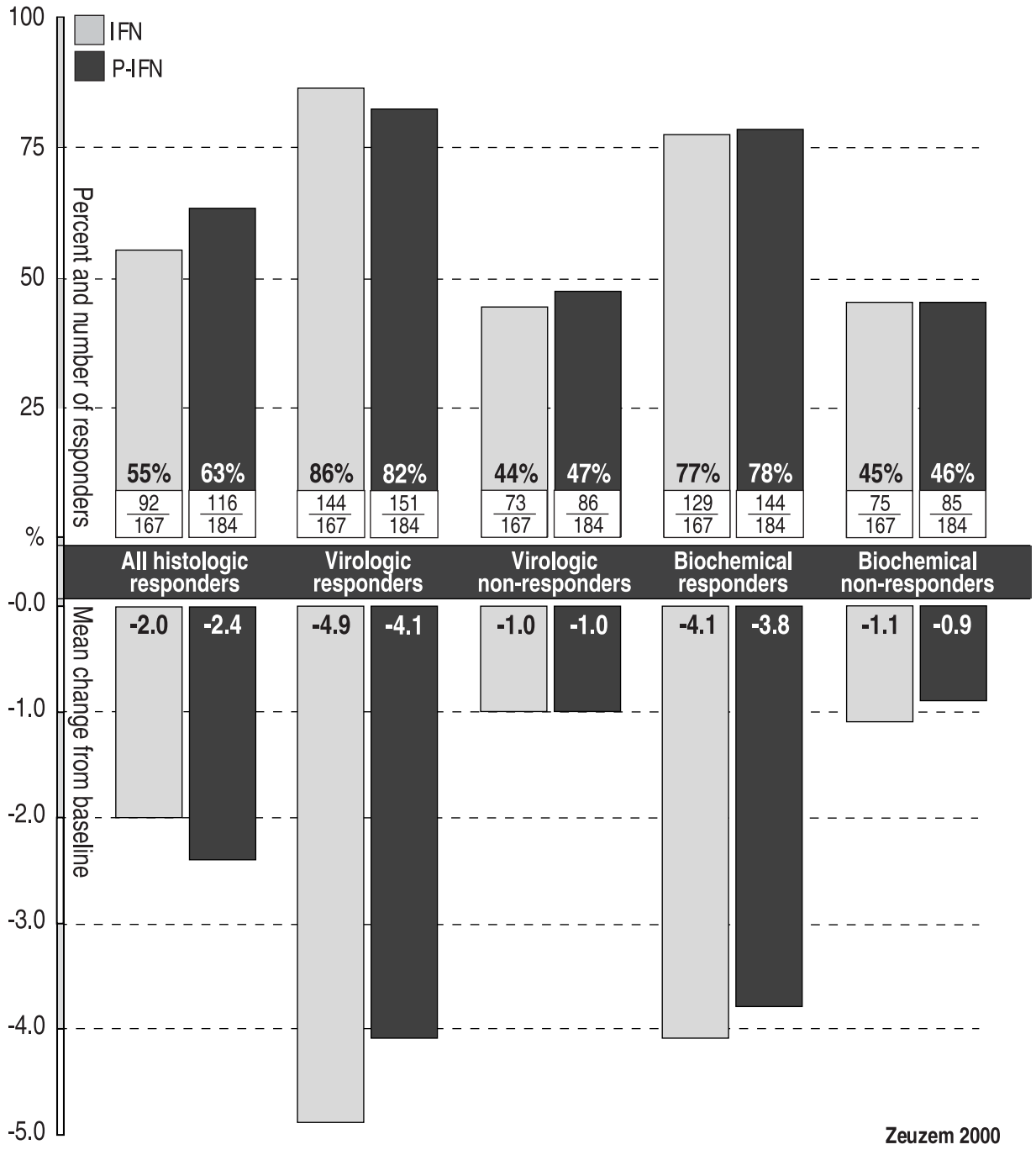
- Six million units of standard interferon alfa-2a thrice weekly for 12 weeks, continuing on a lower dose of three million units thrice weekly for 36 weeks (total course of therapy: 48 weeks); or
- Pegylated interferon alfa-2a (Pegasys ®) 180 μg once weekly for 48 weeks.

Figure 19. End-of-Treatment Response, Sustained Virological Response, and Biochemical Response by Treatment Regime



*P=0.001 for comparison of pegylated interferon vs. standard at 48 and 72 weeks, as well as for sustained biochemical response.

Figure 20. Histological Response at Week 72 from Paired Biopsy Specimens* by HAI.



*A subgroup of 351 (66%) participants had paired baseline and post-treatment liver biopsies (184 received pegylated interferon and 167 received standard interferon). Biopsies were evaluated with the Knodell Histological Activity Index (HAI).

Adverse events, dose reductions, and discontinuations were similar across arms. The adverse events reported in Table 12 occurred in at least 10% of study participants.

Table 12. Adverse Events by Treatment Regimen

Adverse Events	IFN	P-IFN
Headache	66% (173/261)	60% (166/265)
Fatigue	65% (170/261)	60% (160/265)
Pyrexia (fever)	52% (135/261)	37% (99/265)
Myalgia	43% (111/261)	42% (110/265)
Rigors	43% (112/261)	27% (72/265)
Alopecia	37% (96/261)	27% (72/265)
Nausea	35% (91/261)	21% (55/265)
Insomnia	24% (62/261)	18% (48/265)
Depression	23% (59/261)	16% (43/265)
Decreased appetite	21% (55/261)	20% (53/265)
Diarrhea	20% (53/261)	19% (51/265)
Dizziness	16% (42/261)	23% (60/265)
Upper abdominal pain	14% (37/261)	13% (35/265)
Vomiting	12% (32/261)	6% (16/265)
Pruritus	12% (32/261)	18% (49/265)
Impaired concentration	11% (29/261)	5% (14/265)
Cough	10% (25/261)	9% (25/265)
Nasopharyngitis (inflammation of nasal passages and pharynx)	8% (22/261)	11% (28/265)
Inflammation at injection site	7% (17/261)	10% (27/265)

Zeuzem 2000

Table 13. Dose Modifications and Discontinuations

	IFN	P-IFN
Discontinuations	10% (27/261)	7% (19/265)
Dose modifications*	18% (47/261)	19% (51/265)
Due to adverse events	11% (30/261)	8% (21/265)
Due to laboratory abnormalities	9% (24/261)	14% (37/265)

Zeuzem 2000

* Some individuals had adverse events and laboratory abnormalities.

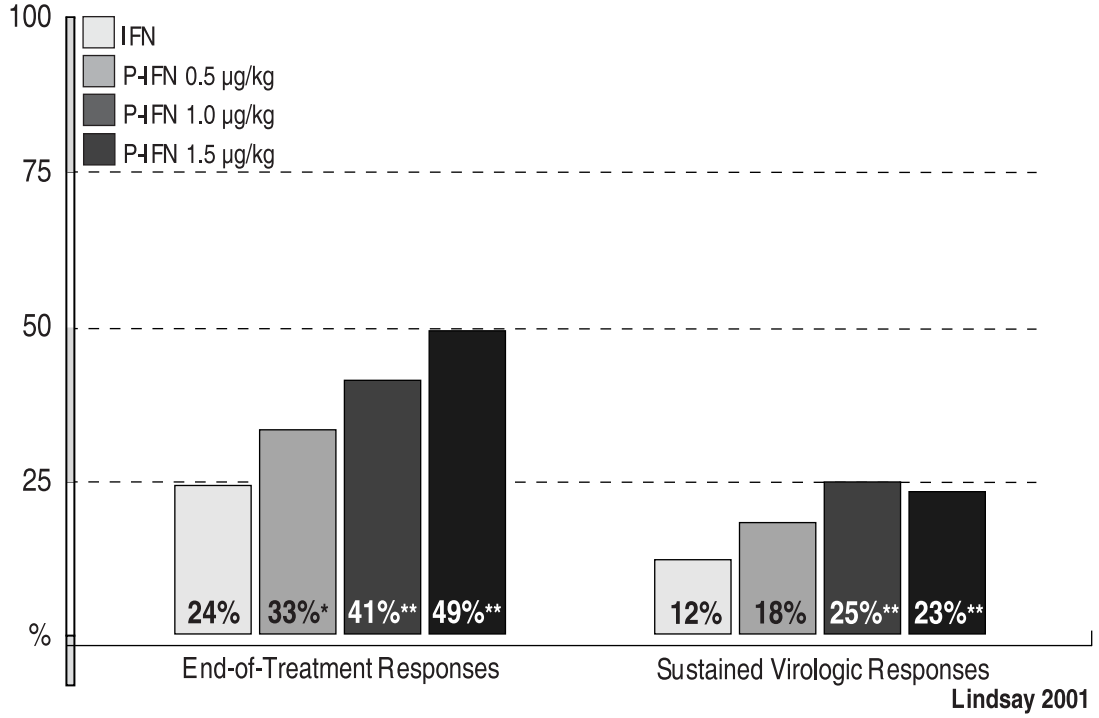
The Lindsay Data

In a study of 159 individuals with chronic hepatitis C, Lindsay and colleagues compared three different doses of pegylated interferon alfa-2b (Peg-Intron®) to a fixed dose of standard interferon. Participants were randomized to one of four arms:

- Pegylated interferon alfa-2b, 0.5 μg/kg once weekly;
- Pegylated interferon alfa-2b, 1.0 μg/kg once weekly;
- Pegylated interferon alfa-2b, 1.5 μg/kg once weekly; or
- Standard interferon alfa-2b, 3 MIU thrice weekly.

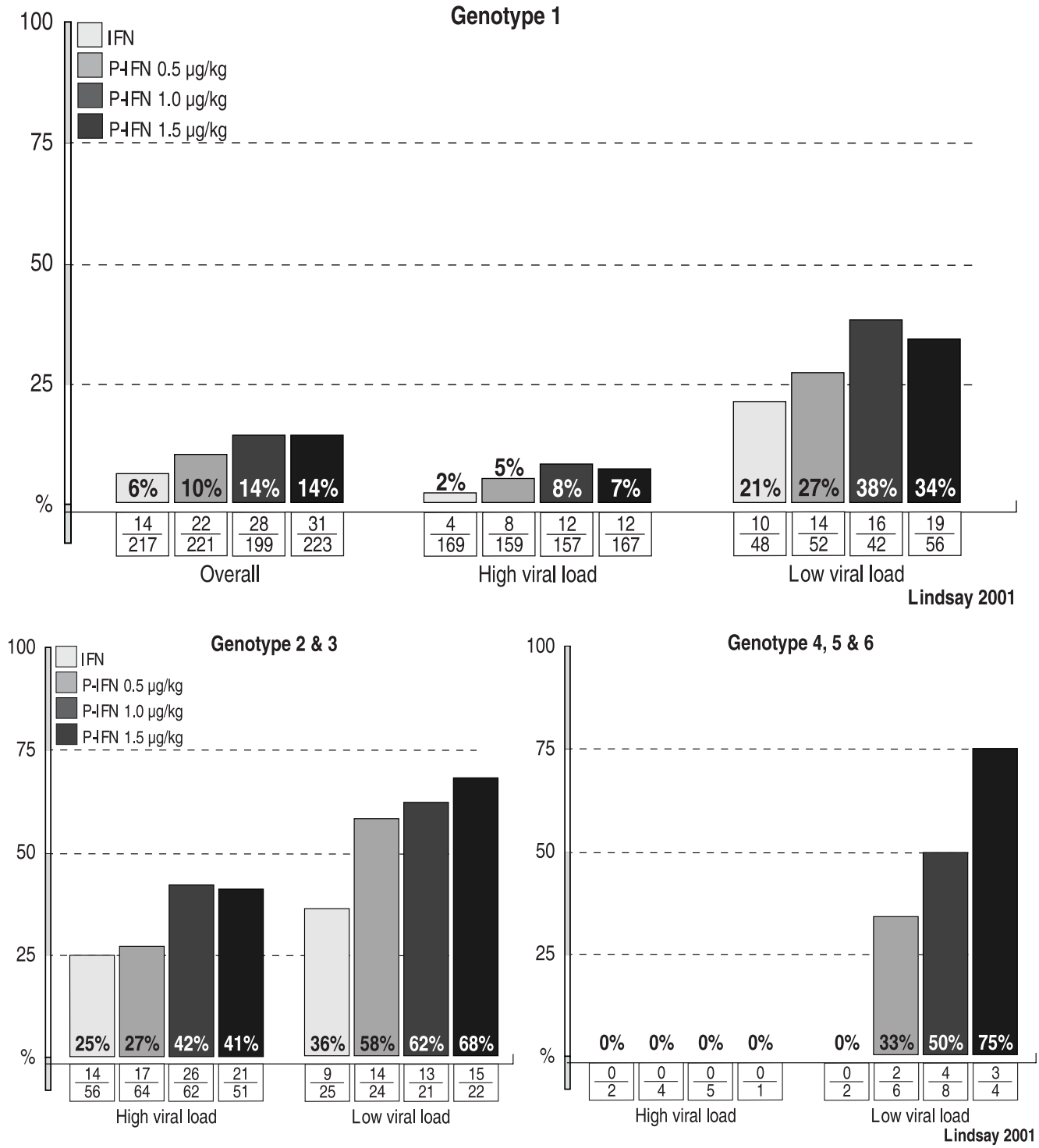
Virological responses at the end of treatment were significantly greater in those who received the two higher doses of pegylated interferon (1.0 and 1.5 μg/kg). Responses through week 48 were dose-dependent; by week 72, the discrepancy in response rates between the two higher doses disappeared, due to high rates of post-treatment relapse. The authors attributed this discrepancy to two factors: higher relapse rates for those with genotype 1 who were treated with 1.5 μg/kg vs.1.0 μg/kg (66% (57/87) and 46% (23/50) respectively; P=0.025); and a greater proportion of participants with genotype 1 in the 1.5 μg/kg arm (73% vs. 67% for the other two arms; P=0.09). Relapse rates among participants with genotypes 2 and 3 were similar (36% in the 1.0 μg/kg arm and 38% in the 1.5 μg/kg arm).

Figure 21. End-of-Treatment Response Rate and Sustained Virological Response Rate



*P=0.01 for P-IFN 0.5.
**P≤ 0.001 for P-IFN 1.0 and P-IFN 1.5 at ETR and for SVR.

Figure 22. Sustained Virological Response by Dose and Formulation of Interferon, Baseline HCV RNA and Genotype



Paired liver biopsy specimens were available from 61% (744/1219) of study participants. The proportion of individuals with a histological response to treatment, as well as the degree of improvement, was similar across all arms (47% to 50%; mean decreases of -1.2 to -1.8 by the Knodell Histologic Activity Index). Although histological improvement was more frequent among those with an SVR (77% to 90%), 33% to 46% of relapsers and 31% to 41% of non-responders achieved histological improvement.

Table 14. Histological Response by Knodell HAI Scoring System: Mean Changes from Baseline

Treatment Outcome	Histologic Responders	HAI (mean changes from baseline)
SVR	77% to 90%	-4.0 to -5.0
Relapsers	33% to 45%	-0.2 to -0.9
Non-responders	31% to 41 %	-0.3 to -0.7

Lindsay 2001

It is encouraging that a percentage of virological and biochemical relapsers and non-responders were able to achieve some degree of improvement in liver histology from pegylated interferon monotherapy, although longer follow-up is needed to assess the durability and clinical value of such improvements.

Although the virological response rates seen with pegylated interferons are an improvement over standard interferon, the side effects are still considerable.

Table 15. Adverse Events by Treatment Regimen

Adverse Events	IFN	P-IFN 0.5 µg/kg	P-IFN 1.0 µg/kg	P-IFN 1.5 µg/kg
Headache	19% (58/303)	19% (61/315)	21% (64/297)	21% (64/304)
Fatigue	14% (43/303)	16% (51/315)	15% (45/297)	16% (50/304)
Chills	11% (33/303)	11% (34/315)	13% (40/297)	14% (44/304)
Fever	10% (30/303)	11% (31/315)	15% (45/297)	14% (44/304)
Myalgia	17% (53/303)	15% (48/315)	18% (54/297)	20% (61/304)
Musculoskeletal pain	7% (22/303)	6% (19/315)	9% (28/297)	6% (20/304)
Nausea	6% (20/303)	7% (21/315)	9% (26/297)	8% (25/304)
Anorexia	5% (17/303)	3% (10/315)	7% (20/297)	8% (25/304)
Irritability	8% (24/303)	6% (19/315)	6% (18/297)	5% (17/304)
Insomnia	7% (23/303)	5% (17/315)	7% (23/297)	6% (20/304)
Alopecia	7% (22/303)	6% (20/315)	7% (22/297)	11% (34/304)
Injection site inflammation	5% (16/303)	14% (44/315)	14% (42/297)	13% (40/304)

Lindsay 2001

Leukocyte, neutrophil, and platelet counts decreased in all arms initially, stabilized after the first few weeks of treatment, and returned to baseline after treatment. Dose reductions for neutropenia occurred more frequently in the 1.5 µg/kg arm (5% vs. 2–3%).

Dose reductions for thrombocytopenia occurred more frequently in the pegylated interferon arms (2–3% vs. 0.3% for standard interferon). Dose reductions occurred most frequently with the two higher doses of pegylated interferon. Discontinuations were similar across the pegylated interferon arms (9–11%), and higher than those in the standard interferon arm (6%) (Lindsay 2001).

Table 16. Discontinuations and Dose Reductions by Dose and Formulation of IFN

	IFN	P-IFN 0.5 µg/kg	P-IFN 1.0 µg/kg	P-IFN 1.5 µg/kg
Discountinuations	1.9% (6/303)	2.8% (9/315)	3.7% (11/297)	2.9% (9/304)
Dose Reductions	1.9% (6/303)	2.8% (9/315)	4.7% (14/297)	6.2% (19/304)

Lindsay 2001

Unresolved Dosing Issues: The Formann Data

The rationale for recommending a different dose of pegylated interferon alfa-2b (Peg-Intron®) for monotherapy (1.0 µg/kg) than that for use in combination with ribavirin (1.5 µg/kg) is unclear. Formann and colleagues randomized 20 individuals to receive 1.0 µg/kg of Peg-Intron® either once or twice weekly for four weeks. Blood levels of Peg-Intron® were below the level of detection by day seven in all but one of the once-weekly dosing group. Those who were randomized to receive twice-weekly dosing had constantly detectable levels of drug. Throughout the four-week induction period, members of the once-weekly group had higher levels of HCV RNA. Viral loads appeared to increase as drug levels decreased. At day 28, 5/10 of the twice-weekly dosing group had undetectable HCV RNA vs. 3/10 of the once-weekly dosing group (Formann 2002). This has raised concern about the recommended dose of 1.0 µg/kg Peg-Intron® for monotherapy; it may be suboptimal.

The Reddy Data

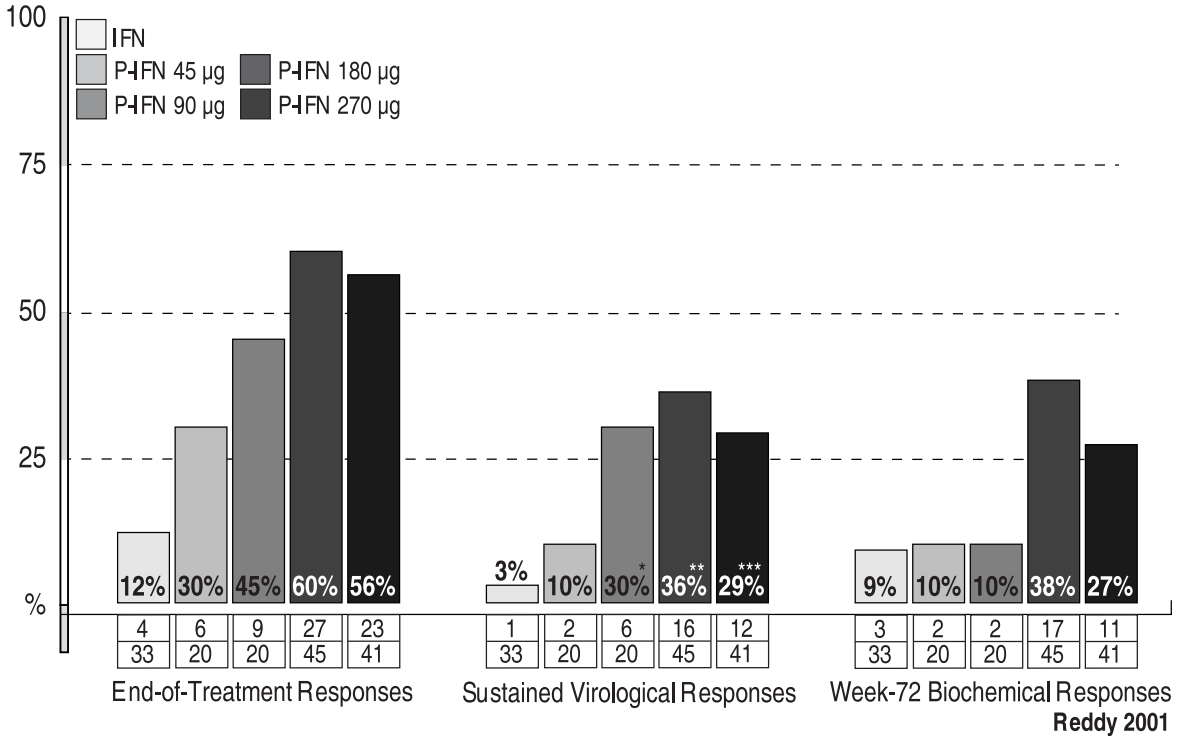
Pegylated interferon alfa-2a (Pegasys®) is not dosed by weight. Dosing for subsequent clinical trials of pegylated interferon alfa-2a was determined by Reddy and colleagues in a dose-ranging study completed by 122 of 159 original participants. The high discontinuation rates in the 180 and 270 µg arms (22% and 20%, respectively) may be attributable to the original protocol design, which initially did not allow dose modifications. Dose modification guidelines were not instituted until several months after the study opened (Reddy 2001).

Participants were randomized to receive either:

- Pegylated interferon alfa-2a, 45 µg once weekly, for 48 weeks;
- Pegylated interferon alfa-2a, 90 µg once weekly, for 48 weeks;
- Pegylated interferon alfa-2a, 180 µg once weekly, for 48 weeks;
- Pegylated interferon alfa-2a, 270 µg once weekly, for 48 weeks; or
- Standard interferon alfa-2a, 3 MIU thrice weekly, for 48 weeks.

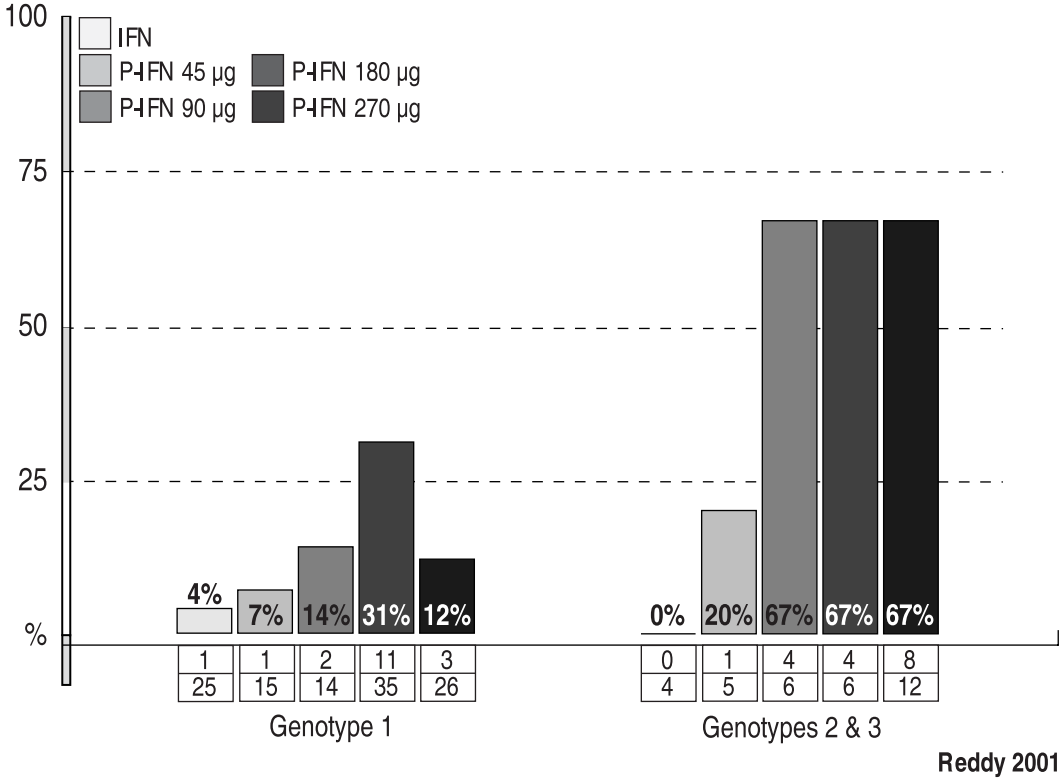
End-of-treatment and week-72 virological response rates were significantly greater in the pegylated interferon dosing arms of 90, 180, and 270 µg.

Figure 23. End of Treatment Response, Sustained Virological Response, and Week-72 Biochemical Response by Dose and Formulation of IFN



All P values are vs. IFN; *P=0.009 for P-IFN 90 µg vs. IFN; **P=0.006 P-IFN 180 µg vs. IFN; ***P=0.004 P-IFN 270 µg vs. IFN.

Figure 24. Sustained Virological Response by HCV Genotype and Dose and Formulation of IFN



The standard interferon arm included more individuals with HCV genotype-1 infections, as well as a higher mean HCV RNA and a slightly larger proportion of participants with bridging fibrosis, which may have contributed to its poorer response rate. In addition, the difference in SVR between the 90 μg arm and the 180 μg arm was relatively narrow. It is unclear whether this may be attributed to a larger proportion of individuals with favorable prognostic factors in the 90 μg arm (genotype non-1 infections, lower baseline HCV RNA levels, and fewer individuals with bridging fibrosis) or because the efficacy of the 90 μg and the 180 μg doses may be roughly equivalent. No further increase in efficacy was observed with the highest dose of pegylated interferon.

Overall, improvements in liver histology (based on paired biopsy samples from a proportion of participants) were similar across groups, but median improvements were greatest in the arm receiving pegylated interferon 180 μg (-3.0). Histological response rates among virological non-responders ranged from 42% to 60% in the pegylated interferon arms vs. 55% in the standard interferon arm.

Table 17. Adverse Events by Dose and Formulation of IFN*

Adverse Events	IFN	P-IFN 45 μg	P-IFN 90 μg	P-IFN 180 μg	P-IFN 270 μg
Fatigue	70% (21/30)	70% (14/20)	85% (17/20)	67% (30/45)	70% (28/40)
Headache	60% (18/30)	40% (8/20)	35% (7/20)	58% (26/45)	48% (19/40)
Myalgia	63% (19/30)	40% (8/20)	65% (13/20)	31% (14/45)	48% (19/40)
Rigors	47% (14/30)	5% (1/20)	20% (4/20)	47% (21/45)	50% (20/40)
Nausea	47% (14/30)	45% (9/20)	15% (3/20)	44% (20/45)	30% (12/40)
Depression	10% (3/30)	30% (6/20)	35% (7/20)	27% (12/45)	38% (15/40)
Diarrhea	20% (6/30)	25% (5/20)	25% (5/20)	31% (14/45)	33% (13/40)
Irritability	13% (4/30)	35% (7/20)	20% (4/20)	29% (13/45)	33% (13/40)
Injection site inflammation	20% (6/30)	35% (7/20)	30% (6/20)	24% (11/45)	25% (10/40)
Insomnia	23% (7/30)	25% (5/20)	5% (1/20)	33% (15/45)	30% (12/40)
Arthralgi	23% (7/30)	20% (4/20)	40% (8/20)	18% (8/45)	30% (12/40)
Pyrexia	30% (9/30)	15% (3/20)	10% (2/20)	24% (11/45)	28% (11/40)
Alopecia	20% (6/30)	5% (1/20)	30% (6/20)	22% (10/45)	25% (10/40)
Upper abdominal pain	17% (5/30)	30% (6/20)	10% (2/20)	18% (8/45)	28% (11/40)
Dizziness	23% (7/30)	10% (2/20)	20% (4/20)	13% (6/45)	18% (7/40)
Impaired concentration	7% (2/30)	10% (2/20)	20% (4/20)	7% (3/45)	30% (12/40)
Dermatitis (skin inflammation)	7% (2/30)	15% (3/20)	0% (0/20)	13% (6/45)	28% (11/40)
Pain	13% (4/30)	20% (4/20)	0% (0/20)	20% (9/45)	13% (5/40)
Decreased appetite	7% (2/30)	15% (3/20)	20% (4/20)	16% (7/45)	13% (5/40)
Back pain	17% (5/30)	0% (0/20)	15% (3/20)	16% (7/45)	15% (6/40)
Pain in limb	13% (4/30)	15% (3/20)	25% (5/20)	9% (4/45)	8% (3/40)
Vomiting	17% (5/30)	20% (4/20)	0% (0/20)	16% (7/45)	3% (1/40)
Pruritus	3% (1/30)	10% (2/20)	15% (3/20)	11% (5/45)	13% (5/40)

Reddy 2001

* The adverse events listed were seen in at least 10% of study participants.

Table 18. Discontinuations by Dose of and Formulation of IFN

	IFN	P-IFN 45 µg	P-IFN 90 µg	P-IFN 180 µg	P-IFN 180 µg
Discountinuations	9%	10%	0%	22%	22%

Reddy 2001

The highest-dose (270 µg) arm had a greater incidence of dose modification because of laboratory abnormalities or adverse events than did the 180 µg group (53% vs. 31%). It is unfortunate that the investigators did not consider using a dose of 135 µg. Offering this dose may have resulted in fewer adverse events, dose modifications, and treatment discontinuations while offering efficacy similar to that of the 180 µg dose. Data from a dose-ranging study comparing the efficacy of pegylated interferon alfa-2a 180 µg to 135 µg (using standard interferon as a comparator) found that both doses yielded an SVR of 28% (vs. 11% for standard interferon), although histological improvement occurred more frequently in the 180 µg arm (58% vs. 48%) (Pockros 2001).

Long-Term Benefits of Hepatitis C Treatment

Interferon can slow or halt HCV disease progression in some individuals, thus treatment may decrease liver-related mortality among people with hepatitis C. Imazeki and colleagues retrospectively analyzed data from 459 people with hepatitis C, 104 untreated, over an eight-year interval. They found an overall reduction in the risk of liver-related death among treated persons. Although the decrease was greater in sustained virological responders (RR, 0.030; 95% CI, 0.003–0.267; P=0.0017), it also decreased among virological non-responders (RR, 0.257; 95% CI, 0.108–0.609; P=0.020) (Imazeki 2003).

Although the duration of follow-up and baseline participant characteristics differ widely across studies of the long-term effects of interferon, the data suggest that among individuals who achieve an SVR or a biochemical response to treatment, fibrosis progression is slowed or arrested and, in some cases, pre-treatment liver damage can be reversed (Cammá 2004; Lau 1998; Marcellin 1997; Schvarcz 1999; Shiatori 2000; Shindo 2001; Yabuuchi 2000; Yoshida 2002). Lau and colleagues followed ten individuals for six to thirteen years after completion of HCV treatment (with varying regimens of interferon alfa-2b). Half of the group achieved SVR; the other five were non-responders. Liver biopsies were performed five to eleven years after therapy. All five of the sustained responders had no detectable HCV RNA in their serum or their liver at final follow-up. Biopsy samples from all five responders reflected improvements over baseline and end-of-treatment scores for fibrosis and inflammation; one individual had normal liver tissue and the other four had non-specific, mild inflammation without significant fibrosis. All five of the non-responders had detectable HCV RNA at final follow-up, and two had increased fibrosis scores. One non-responder developed hepatocellular carcinoma (HCC) five years after treatment and had a liver transplant, while another progressed to decompensated liver disease and died from an intracerebral bleed while awaiting transplantation (Lau 1998).

Marcellin and colleagues evaluated the long-term benefit of interferon among 80 individuals who achieved sustained virological and biochemical responses to interferon treatment. Follow-up ranged from 1.0 to 7.6 years. HCV RNA remained undetectable in 96%, and 93% maintained persistently normal liver enzyme levels. Before treatment, 60% experienced fatigue; after treatment,

none reported fatigue. Baseline liver biopsy samples were available from all 80 participants, and at least one post-treatment biopsy was performed on 69 individuals between one and six years after completion of treatment. Normal—or nearly normal—liver histology was observed after treatment in 62%, while 94% had an improvement in liver histology. No new cases of cirrhosis were diagnosed after treatment. Of the five individuals with pre-treatment cirrhosis, four had post-treatment biopsies. An improvement was seen in two; disease progression without liver decompensation or hepatocellular carcinoma was found in the other two (increases of one and two points on the Knodell HAI, respectively) (Marcellin 1997).

Although achieving a sustained virological response increases the likelihood of histological benefit, a sustained biochemical response to treatment appears to reduce the risk of HCV disease progression. Shindo and colleagues studied the pre- and post-treatment liver histology of 250 individuals treated with standard interferon and a control group of 89 untreated individuals. Follow-up ranged from 8 to 11 years post-treatment. The treated cohort was categorized by response to therapy as: complete responders (defined as sustained virological and sustained biochemical response), biochemical responders, relapsers, and non-responders. The annual incidence of cirrhosis was significantly lower in complete responders, biochemical responders, and relapsers than in an untreated control group (P=0.0001).

Table 19. Annual Incidence of Cirrhosis and HCC among Responders, Relapsers, Non-Responders, and Untreated Controls

Treatment Response	% of total	Annual Incidence of	
		Liver Cirrhosis	Hepatocellular Carcinoma
Complete responders	27% (67/250)	0%	0.37%
Biochemical responders	10% (26/250)	0%	0.50%
Relapsers	28% (70/250)	1%	0.80%
Non-responders	35% (87/250)	14.9%	5.5%*
Untreated controls	89	6.4%	1.2%

Shindo 2001

*P=0.0001 for complete responders, biochemical responders, relapsers, and controls vs. non-responders.

Complete responders had improvements in the grade (amount of disease activity) and stage (structural progression of disease) of liver histology at the end of treatment. Grading scores continued to decrease at one and two years after treatment, while staging scores decreased at one year after treatment and then stabilized. Biochemical responders had decreases in grading and staging scores by the end of treatment, but their scores did not change subsequently (Shindo 2001).

Fibrosis does not invariably improve after hepatitis C treatment. Shiratori and colleagues performed a retrospective cohort study, assessing post-treatment changes in fibrosis and inflammatory activity in biopsy samples from 487 interferon-treated individuals and 106 untreated controls. Liver biopsy was performed within six months of treatment initiation and 1–10 years (median, 3.7) after completion of treatment. Regression of fibrosis and improvement in histological activity occurred most frequently among those who achieved sustained virological responses, although some relapsers experienced histological improvement as well (Shiratori 2000).

Table 20. Post-Treatment Changes in Fibrosis among Sustained Responders and Relapsers, Plus Untreated Controls

Treatment Response	Fibrosis Activity		
	Regression	No Change	Progression
Sustained responders	59% (108/183)	40% (73/183)	1% (2/183)
Relapsers	19% (57/304)	57% (173/304)	24% (74/304)
Untreated controls*	5% (5/106)	57% (61/106)	38% (40/106)

Shiratori 2000

*Lower baseline ALT level, milder histologic activity and fibrosis than treated cohort

Table 21. Post-Treatment Changes in Disease Activity among Sustained Responders and Relapsers, Plus Untreated Controls

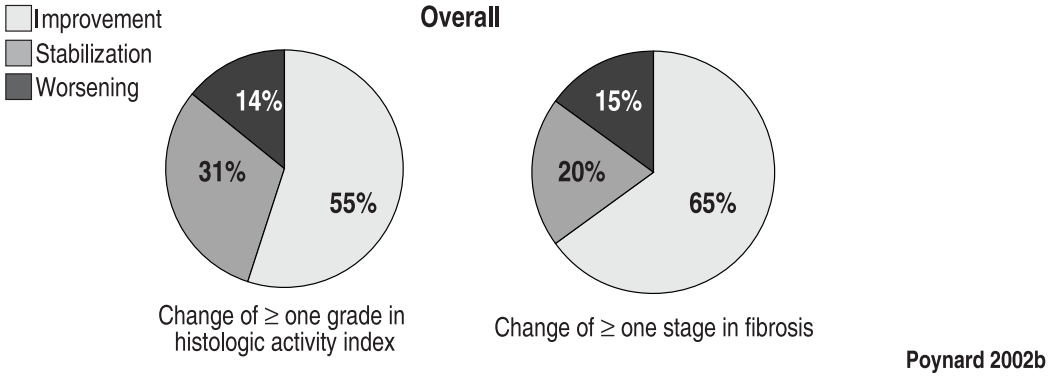
Treatment Response	Inflammatory Disease Activity		
	Decreased	Stable	Increased
Sustained responders	89% (162/183)	10% (19/183)	1% (2/183)
Relapsers	32% (98/304)	49% (148/304)	19% (58/304)
Untreated controls*	20% (21/106)	58% (62/106)	22% (23/106)

Shiratori 2000

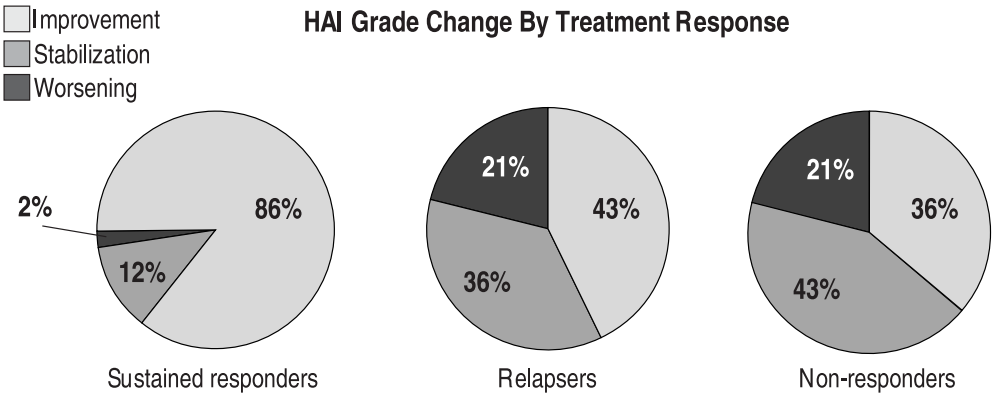
* Lower baseline ALT level, milder histological activity and fibrosis than treated cohort

Poynard and colleagues used a modeled estimate of fibrosis progression (see Chapter II, Natural History of Hepatitis C) to compare baseline and post-treatment changes in fibrosis progression and disease activity by treatment regimen. Data were pooled from four randomized treatment trials with 3,010 participants. They examined rates of pre- and post-treatment fibrosis progression, liver histology after therapy, and histological response by regimen. The mean duration between baseline and post-treatment biopsies was 20 months.

Figure 25. Changes in Grade of Histological Activity and Fibrosis Stage



Poynard 2002b



Poynard 2002b

Improvements in the histological activity grade occurred most frequently among those who received pegylated interferon alfa-2b 1.5 μg/kg plus high-dose ribavirin (73%), and least frequently (39%) among those who received 24 weeks of standard interferon alfa-2b. Worsening of fibrosis occurred least frequently in those who received pegylated interferon alfa-2b 1.5 μg/kg with high-dose ribavirin (8%), and occurred most frequently among those treated with 24 weeks of standard interferon monotherapy (23%).

Among cirrhotics, 49% (75/153) had improvement in fibrosis after treatment. All of them received 48 weeks of standard interferon alfa-2b, with or without ribavirin. Improvement from stage 4 to stage 3 was observed in 23 individuals; from stage 4 to stage 2 in 26; and from stage 4 to stage 1 in 23. Three individuals improved by four stages (to stage 0; no remaining fibrosis) (Poynard 2002b). Although this is a promising report, it is preliminary, and may be limited by the use of estimated fibrosis progression rates per year, since fibrosis progression is not always linear.

Cammà and colleagues performed a meta-analysis of data from three HCV treatment trials, to examine the effect of pegylated interferon alfa-2a on liver histology, using baseline and post-treatment biopsy samples from 1,013 people. All were treated for 48 weeks with pegylated interferon alfa-2a or standard interferon. Overall, 280 achieved SVR (215 from pegylated interferon vs. 65 from standard interferon; P=0.001). Reduction in fibrosis was most likely among those treated with pegylated interferon (P=0.04) and sustained virological responders (P<0.001). Sustained virological response was significantly associated with reductions in disease activity (P<0.00001). Relapse was associated with improvement in fibrosis (P=0.0007) and disease activity (P=0.004), while no significant changes were observed among virological non-responders (Cammà 2004).

Table 22. Changes in Fibrosis and Disease Activity After Treatment with Standard or Pegylated Interferon

Treatment Response	Inflammatory Disease Activity		
	Improved	Stabilized	Worsened
Fibrosis (Staging)	25.7% (261/1013)	63.6% (645/1013)	10.5% (107/1013)
Disease Activity (Grading)	48.4% (491/1013)	34.5% (350/1013)	16.9% (172/1013)

Cammà 2004

Longer-term follow-up will reveal the durability and clinical benefits of improvements in grading and staging of liver disease.

Treatment of Acute Hepatitis C Infection

It is difficult to identify cases of acute hepatitis C infection for many reasons. The incidence of new infections—especially from transfusions and blood products—has decreased and the majority of acute HCV infections are asymptomatic. Fewer than 25% of individuals with acute HCV infection seek medical attention. Clinicians may overlook HCV infection if it is not suspected (Villano 1999). In addition, there is not a specific diagnostic test to identify acute HCV infection (see Chapter IV, Diagnostics). Despite these obstacles, several studies have examined different doses and durations of interferon therapy in individuals with acute HCV. A meta-analysis of data from four randomized, controlled trials of acute, post-transfusion hepatitis C, all treated with interferon alfa-2b revealed a 29% increase in SVR among treated vs. untreated individuals (P=0.00007) (Alberti 2002). In three of these studies, the interferon dose was identical: three MIU of interferon alfa-2b, thrice weekly, for twelve weeks (Hwang 1994; Lampertico 1994; Viladomiu 1992). Two treatment regimens were used in the remaining study. Eight participants received 3 MIU daily for one week, which was followed with 3 MIU every other day for eleven weeks; another group of eight participants were given 3 MIU every other day for twelve weeks (Li 1993). The response rates from these studies are not much different from the response rates in chronic hepatitis, with almost two-thirds of the treated individuals developing chronic hepatitis.

More promising results came from two uncontrolled studies of interferon therapy during acute-phase hepatitis C in which 90% and 98% of participants achieved sustained virological responses. Vogel and colleagues treated 24 individuals with acute hepatitis C with 10 MIU of subcutaneous (SQ) interferon alfa-2b per day until liver enzyme levels reached normal levels (18–43 days). Pre-treatment ALT levels ranged from 531 to 1,940 IU/liter, with a mean of 1055; normal ALT was considered to be <22 IU/liter. Twenty-two of 24 participants completed treatment; 18 (90%) of these individuals remained virus-free during a follow-up interval of 18.65 ± 9.7 months (Vogel 1996). Jaeckel and colleagues treated 44 individuals with subcutaneous injections of 5 MIU of interferon alfa-2b per day for four weeks, followed with thrice weekly dosing for 20 more weeks. Treatment was initiated at an average of 89 days (with a range of 30–112) after infection. All but one individual completed treatment. One individual was re-treated (with interferon alfa-2b and ribavirin) 89 days after finishing study treatment. After six months of follow-up, 98% (43/44) had an undetectable HCV-RNA level (including the individual who discontinued treatment at week 12 and the individual undergoing re-treatment) (Jaeckel 2001).

It is important to note that both studies were uncontrolled. Without a randomized, untreated control group, it is not possible to determine how many study participants would have achieved spontaneous viral clearance without undergoing treatment. Other factors may have had contributed to the high rates of a viral clearance: homogeneity of study participants—many of whom were symptomatic and jaundiced (both of which have been associated with higher rates of spontaneous viral clearance)—and the mode of acquisition. In these two studies, all of the participants acquired their infections from occupational or nosocomial exposures, injection drug use, sexual contact, or sporadic (unknown) means. HCV infections acquired from transfusions appear to have a higher rate of chronicity than those acquired by other means (Alberti 2002). In addition, the follow-up periods may have been too brief, or RNA testing too infrequent to detect intermittent viremia. HCV RNA may have been present in levels below the threshold of detection; Jaeckel and colleagues used an assay with a lower limit of detection of 600 copies, the most sensitive

available at the time (Jaeckel 2001).

Gerlach and colleagues identified 60 individuals with acute hepatitis C over a seven-year interval. Each was offered HCV treatment at diagnosis; ten individuals either declined or were ineligible (due to active injection drug use or other medical conditions) and 24 others achieved spontaneous viral clearance before HCV treatment was initiated. Of the 26 who were treated, 21 (81%) achieved SVR. Risk factor and interval between diagnosis and initiation of treatment differed among individuals, as did the regimen and duration of therapy (Gerlach 2003).

Table 23. Acute HCV: Risk Factor, Interval from Diagnosis to Treatment, HCV Genotype, Regimen and Response

Risk Factor	Genotype	Months from Diagnosis	TX Regimen	TX Duration
Sustained Virologic Responders (N=21)				
IV drug use	1b	4.2	IFN 3 MU 3 x week + RBV	50 weeks
IV drug use	1b	26.2	IFN 5 MU/3 MU, 3 x week	52 weeks
IV drug use	1b	3.4	P-IFN 80µg 1 x week + RBV	14 weeks
IV drug use	2a	6.6	P-IFN 80µg 1 x week + RBV	23 weeks
IV drug use	3	7.6	IFN 5 MU 3 x week	34 weeks
IV drug use	3	6.5	IFN 5 MU 3 x week + RBV	50 weeks
IV drug use	Unknown	1.0	IFN 3 MU 3 x week + RBV	52 weeks
Sexual	1a	5.5	IFN 5 MU 3 x week + RBV	26 weeks
Sexual	1b	2.4	IFN 3 MU 3 x week	29 weeks
Medical procedure	1b	9.7	IFN 5 MU/3MU 3 x week	38 weeks
Medical procedure	3	12.9	P-IFN 100µg 1 x Week	46 weeks
Surgery	3b	1.9	P-IFN 80µg 1 x week + RBV	25 weeks
Dental surgery	1a	3.7	IFN 5 MU 3 x week + RBV	26 weeks
Unknown	1b	10	IFN 5 MU 3 x week + RBV	61 weeks
Unknown	1b	0.9	IFN 5 MU 3 x week	17 weeks
Unknown	2a	7.1	IFN 3 MU 3 x week + RBV	52 weeks
Unknown	3	1	IFN 3 MU 3 x week	35 weeks
Unknown	3	12.6	IFN 5 MU 3 x week	50 weeks
Needlestick	1a	5.9	IFN 5 MU 3 x week + RBV	53 weeks
Needlestick	1b	0	IFN 5 MU 3 x week + RBV	26 weeks
Needlestick	1b	0.3	IFN 5 MU 1 x day + RBV P-IFN 100µg 1 x week +RBV	51 weeks
Relapsers (N=2)				
Sexual	1a	8.6	IFN 3 MU 3 x week	37 weeks
Medical procedure	1a	0.4	P-IFN 80µg 1 x week	36 weeks
Non-responders (N=3)				
Surgery	1b	20.5	IFN 3 MU 3 x week	31 weeks
Surgery & transfusion	4	3.3	IFN 3 x 6 MU	26 weeks
Unknown	1a	11.6	IFN 3 MU 3 x week + RBV	23 weeks

Gerlach 2003

Amid the compelling evidence that treating acute hepatitis C infection is beneficial, questions remain about the dosing and duration of treatment, choice of therapeutic agent(s), and determination of the need for treatment. Optimal dose and duration of standard interferon therapy have yet to be identified, and pegylated interferons have not been adequately explored as treatments for acute HCV. The higher response rates to pegylated interferon in chronic hepatitis C suggest that they will be more effective against acute hepatitis C. Information about dosing from studies of standard interferon may not be applicable to pegylated interferon, because it is difficult to translate the dosage of standard interferon (in millions of international units) into doses of pegylated interferon (in micrograms). Preliminary information suggests that 1.0 μg/kg may be a suboptimal dose of pegylated interferon alfa-2b for treatment of acute HCV (Wiegand 2003). Data on interferon and ribavirin during acute HCV infection are scant.

Determining when to initiate treatment for acute hepatitis C is an important issue. Treatment may not be necessary for those who will achieve spontaneous viral clearance. Identifying these individuals before initiating treatment will spare them the side effects and expense of unnecessary treatment. Findings from a study of twelve individuals with acute HCV indicated a high rate of spontaneous viral clearance relatively soon after exposure and onset of symptoms. Eight individuals achieved spontaneous viral clearance by 74 ± 25.3 days after exposure and 34.7 ± 22.1 days after the onset of symptoms. HCV-RNA levels decreased rapidly in the individuals with viral clearance. In the remaining four individuals HCV-RNA levels stayed high or increased (Hofer 2003). Larghi and colleagues noted longer intervals of detectable HCV RNA among seven acutely infected individuals. Before achieving spontaneous viral clearance, these seven individuals had detectable HCV RNA for between four and thirteen months after infection (Larghi 2002). Larger studies are needed to determine when treatment of acute HCV should be initiated.

Treatment for Relapsers and Non-Responders

As HCV treatments become more effective, options for re-treatment of relapsers and non-responders have increased. The likelihood of achieving an SVR after re-treatment of HCV hinges in part upon the difference in efficacy of the first regimen and any subsequent regimen. Using the identical treatment regimen usually does not improve treatment outcomes; the re-treatment regimen should have superior efficacy to the initial regimen.

Prognostic factors—genotype, baseline HCV RNA—and ability to tolerate HCV treatment influence the likelihood of successful re-treatment. The type of response to the initial course of treatment may also contribute to the success of re-treatment. Relapsers (who become HCV RNA undetectable but do not remain aviremic after completion of treatment) are more likely to achieve an SVR after re-treatment than non-responders (Shiffman 2002a). There are two patterns of non-response to HCV therapy. A partial response indicates a decrease in HCV RNA of >2.0 log and persistently detectable HCV RNA during treatment; a flat response is characterized by a decrease of <2.0 log in HCV RNA while on treatment, which may be an indication of interferon resistance.

Strategies for effective re-treatment have included higher-dose interferon monotherapy, different types of interferon, a longer duration of therapy and re-treatment with a combination of interferon plus ribavirin or pegylated interferon plus ribavirin. Data from two meta-analyses of re-treatment for non-responders to interferon monotherapy report low overall SVR rates (ranging from 13% to

20%). Individuals were re-treated with inteferon plus ribavirin. Reponse rates depended on duration of re-treatment therapy and individual prognostic factors (Cheng 2001; Cummings 2001).

Pegylated Interferon in Relapsers and Non-Responders

End-of-treatment results are available from a study examining responses to re-treatment with 48 weeks of pegylated interferon alfa-2a plus ribavirin in 64 individuals who relapsed after 24 weeks of treatment with the same regimen. The maximum allowable dose for pegylated interferon was 180 μg once weekly; the maximum dose for ribavirin was 1,000–1,200 mg/day. Some individuals received lower doses of one or both drugs based on their experience with each drug during the previous regimen. End-of-treatment results are available from 59 participants who completed 48 weeks of treatment (Goncales 2002). Since all participants achieved undetectable HCV RNA after their initial course of treatment (with the exception of one person, who was withdrawn from this study) the efficacy of re-treatment with the same regimen for a longer interval can be determined only at week 72.

Table 24. HCV-RNA Levels at Week 48 of Re-treatment

	Undetectable	Detectable	Not Tested
Overall (N=59)	90% (53)	5% (3)	5% (3)
Genotype 1 (N=41)	88% (36)	7% (3)	5% (2)
Genotype 2 & 3 (N=14)	93% (13)	0%	7% (1)

Goncales 2002

HALT-C: Treatment in Non-Responders with Advanced Liver Disease

The Hepatitis C Antiviral Long-Term Treatment Trial Against Cirrhosis (HALT-C) is assessing tolerability and rate of SVR in individuals with advanced fibrosis or cirrhosis (Ishak score 3 by liver biopsy; see Chapter IV, Diagnostics) who were non-responders to prior therapy with standard interferon, with or without ribavirin. During the lead-in phase of HALT-C, all participants received 24 weeks of pegylated interferon alfa-2a 180 μg once weekly plus ribavirin (1,000–1,200 mg/day, based on weight). Individuals with detectable HCV RNA after 20 weeks of treatment were rolled into HALT-C. Those with undetectable HCV RNA at week 20 were treated for an additional 28 weeks, then followed for 24 more weeks.

So far, SVR data is available from 604/863 who have completed treatment and follow-up. Overall, 18% (109/604) achieved SVR. Prior interferon monotherapy, genotype 2 or 3, a lower AST:ALT ratio and no cirrhosis were associated with achievment of a sustained virological response. SVR was more likely among those who received ≥ 60% of the ribavirin dose (21% vs. 11%; P=0.05) (Shiffman 2004).

In a sub-group of 212 HALT-C participants who completed therapy by late 2002, the likelihood of SVR was significantly greater in non–African Americans, non-1 genotypes, those with a 2.0 log decrease in HCV RNA at week 12, and persons less than 50 years old (P<0.005 for all). More than half of these the participants had dose reductions of pegylated interferon and/or ribavirin.

Week 24 discontinuations for fatigue, depression, or hematologic abnormalities were reported in 5% (Shiffman 2002b).

Treatment for Compensated Cirrhotics

Cirrhotics may remain stable for several years. During this window, initiation of HCV treatment may delay progression to hepatic decompensation or hepatocellular carcinoma. In a retrospective follow-up of 384 compensated cirrhotics with hepatitis C, the five-year survival probability was 91%, decreasing to 79% at ten years, suggesting that this interval presents a valuable opportunity for HCV treatment (Fattovich 1997).

A retrospective analysis of data from 637 cirrhotics, treated and untreated, found that treatment with interferon—regardless of the outcome—seems to affect the oncogenic mechanisms of HCV. Interferon alfa is active against a number of cancers, including AIDS-associated Kaposi's sarcoma (KS). The International Interferon-a Hepatocellular Carcinoma Study Group identified predictors of progression from compensated cirrhosis to hepatocellular carcinoma (male sex, older age, and signs of portal hypertension) and time from diagnosis of cirrhosis to development of hepatocellular carcinoma. The study compared outcomes of two matched groups, one of 356 untreated cirrhotics and one of 281 cirrhotics treated with interferon. The median duration of therapy was 7 months (range: 3–30 months). Participants were followed for at least three years. The overall risk of progression to HCC was 1.99 for untreated individuals (95% CI, 1.09–3.6; P=0.027), with 66 untreated individuals and 29 treated individuals developing HCC during an interval of 36–250 months. Among cirrhotics with HCV infection, the relative risk of progression to hepatocellular carcinoma among untreated individuals was 3.14 times that of those treated with interferon (95% CI, 1.46–6.80; P=0.004). In a subgroup of cirrhotics who were HCV-antibody-positive and anti-HBV-negative, the risk of progression to hepatocellular carcinoma for untreated individuals was 6.28 times greater (95% CI, 1.65–23.97; P<0.007) (The International Interferon-α Hepatocellular Carcinoma Study Group 1998).

The effect of interferon on the clinical outcomes of 189 cirrhotics was retrospectively assessed by Benvegnù and colleagues during a mean follow-up of 71.5 ± 23.6 months; 7.9% of those who received treatment (88/189) and 21.8% of untreated individuals (101/189) had progressive liver disease (by Child's staging; see Chapter IV, Diagnostics). Hepatocellular carcinoma developed in 5.6% of treated persons vs. 26% of untreated individuals (P<0.001) (Benvegnù 1998).

Imazeki and colleagues retrospectively analyzed the effect of interferon on survival rates of people with hepatitis C. Of the 459 individuals in this study, 104 were untreated. Among cirrhotics, those who achieved SVR had a reduced rate of mortality during the eight-year follow-up. Hepatocellular carcinoma accounted for 25 deaths overall; only one was a sustained virological responder (Imazeki 2003).

There are particular safety concerns for cirrhotics; many are more vulnerable to side effects and adverse events, especially the hematologic toxicities of pegylated interferons. As a result, dose reductions may be more frequent, and the efficacy of treatment may be diminished. For example, there were dose reductions among 83% (44/53) of those participating in an ongoing study of the viral kinetics of pegylated interferon alfa-2a plus ribavirin in cirrhotics (Gane 2002).

Interim data from an HCV treatment trial in people with advanced liver disease (bridging fibrosis or cirrhosis) suggests that full-dose pegylated interferon and weight-based dosing of ribavirin, especially in non-1 genotypes, may increase the likelihood of sustained virological responses. Participants were randomized to receive 48 weeks of treatment with either full-dose (1.5 μg/kg once weekly) or half-dose (0.75 μg/kg once weekly) pegylated interferon alfa-2b, plus 800 mg/day of ribavirin. Sustained virological response data are available from 165 of 210 participants who have completed follow-up (Abergel 2003). No information on adverse events, dose reductions, or discontinuations was provided.

Table 25. Sustained Virological Response by Regimen and Genotype

	P-IFN 0.75 μg/kg		P-IFN 1.5 μg/kg	
	+ RBV > 10.6 mg/kg	+ RBV < 10.6 mg/kg	+ RBV > 10.6 mg/kg	+ RBV < 10.6 mg/kg
Genotypes 1, 4 & 5	17% (6/35)	15% (3/20)	29% (9/31)	26% (5/19)
Genotypes 2 & 3	85% (11/13)	57% (8/14)	91% (21/23)	60% (6/10)

Abergel 2003

A subset of individuals with bridging fibrosis and cirrhosis have participated in large HCV treatment trials. The treatment regimens and study populations differ, so it is difficult to draw conclusions from pooled data.

Table 26. Sustained Virological Response Rate Among Persons With Bridging Fibrosis and Cirrhosis: Subgroup Data From Four Trials

Study	Best SVR Rate	Regimen
Manns 2001	44% (60/136)	P-IFN alfa-2b 1.5mg/kg + RBV 800mg for 48 weeks
Fried 2002a	43% (25/56)	P-IFN alfa-2a 180μg + RBV 1000–1200mg for 48 weeks
Marcellin 2003	49% (38% for genotype 1;72% for non-1)	P-IFN alfa-2a 180μg + RBV 1000–1200mg for 48 weeks
Hadziyannis 2004	41% for genotype 1	P-IFN alfa-2a 180μg + RBV 1000–1200mg for 48 weeks
Hadziyannis 2004	75% for genotype 2 or 3	P-IFN alfa-2a 180μg + RBV 800mg for 24 weeks

The goals of therapy may be different for those with advanced liver disease. Averting liver transplantation, slowing disease progression, and improvement in liver histology may be relevant outcomes in the absence of achieving SVR, although histological response often correlates with virological response. Without long-term follow-up, it is impossible to know if histological improvement and/or viral eradication translate into increased quality of life and survival. Long-term studies of interferon maintenance therapy for non-responders with advanced liver disease are underway.

Treatment for Decompensated Cirrhotics

Individuals with decompensated cirrhosis need treatment urgently, as their five-year survival is 50% (Fattovich 1997). The safety of interferon and ribavirin in decompensated cirrhotics is a significant concern. Individuals with decompensated cirrhosis are at greater risk of life-threatening complications during therapy, such as deteriorating liver function, bone marrow suppression, and infections. Because of these concerns, individuals with decompensated cirrhosis have been excluded from pivotal clinical trials. Data on treatment of decompensated cirrhotics are very limited; there have been no randomized, controlled treatment trials in this population.

Everson and colleagues studied safety, efficacy, and tolerability of a gradually accelerated dosing regimen. This strategy resulted in SVR among 22% (20/91), with 40% (8/20) of those who achieved SVR remaining HCV-RNA-undetectable after liver transplantation. The regimen started with low doses of interferon (1.5 MIU thrice weekly), plus ribavirin (600 mg/day). Doses of each drug were gradually increased every two weeks, as tolerated. Growth factors were used to maintain blood cell counts when needed (Everson 2000). Information on changes in hepatic function, Child-Pugh scoring after treatment (see Chapter IV, Diagnostics), and serious adverse events was not available.

Crippin and colleagues conducted a pilot study of the safety, tolerability and efficacy of interferon with or without ribavirin in individuals with decompensated cirrhosis. Fifteen participants awaiting liver transplantation were randomized to:

- Interferon alfa-2b, 1 MIU/day;
- Interferon alfa-2b, 3 MIU/thrice weekly; or
- Interferon alfa-2b, 1 MIU/day, plus ribavirin 800 mg/day.

At the end of treatment, 33% had undetectable HCV RNA, and 55% had reduced viral loads. During the study, two individuals had liver transplants; both had recurrent hepatitis C. Adverse events were frequent and serious; 20 of the 23 adverse events were serious (severe thrombocytopenia and neutropenia, hepatic encephalopathy, and serious infections). One person died from infectious complications (Crippin 2003). The study was ended because of the frequency of severe adverse events.

Garcia-Retortillo and colleagues treated 30 individuals (13 cirrhotics and 17 with hepatocellular carcinoma) awaiting liver transplantation. Treatment was initiated when the anticipated interval before transplantation was less than five months and continued until transplantation. At the time of transplantation, 9/30 had undetectable HCV-RNA levels and 6/9 remained undetectable after transplantation (median follow-up of 26 weeks; range: 5–60 weeks).

The original regimen was standard interferon alfa-2b (3 MIU daily) plus ribavirin (400 mg every 12 hours). The dose of interferon was reduced in 60% (18/30); the ribavirin dose was reduced in 20% (6/30). Growth factors were given when necessary (G-CSF to 10/30; Epoetin-alfa to 8/30). Treatment was discontinued permanently by four individuals and temporarily by two. There were three serious adverse events: two cases of sepsis and one case of hepatitis. Leukopenia was reported in 18/30, thrombocytopenia in 13/30, and anemia in 5/30 (Garcia-Retortillo 2002b).

Treatment in Liver Transplant Recipients

In the United States, end-stage liver disease resulting from chronic hepatitis C infection is the leading indication for liver transplantation. As of June 30, 2003, 17,001 people were waiting for a liver (http://www.ustransplant.org/facts.html, accessed on 8 April 2004). After liver transplantation, hepatitis C infection of the graft occurs almost universally (Gretch 1995; Terrault 1995; Wright 1992; Zekry 2003). Viral replication begins within hours of liver transplantation (Garcia-Retortillo 2002a).

The overall survival rate at one year after liver transplantation is 85%; at three years, 75.9%; and at ten years, it decreases to 59% (C. M. Smith 2000; United Network for Organ Sharing, 2000). For transplant recipients with hepatitis C, survival rates at one year, three years, and five years are 86.4%, 77.8%, and 69.9%, respectively (Forman 2002). Progression of post-transplant hepatitis C disease varies (see Chapter III, Natural History of HCV in HIV Coinfection; HCV and Immunosuppression). Cirrhosis develops in 10–25% of transplant recipients with recurrent HCV within five years (Everson 2002). Individuals with early recurrence of HCV (less than six months after transplantation) are at greater risk of progression to bridging fibrosis or cirrhosis (Shuhart 1997; Testa 2000).

There are three strategies for treating recurrent hepatitis C: preemptive treatment prior to transplantation, initiating treatment as soon as possible after transplantation, or delaying treatment until post-transplantation hepatitis has recurred. The goals of preemptive treatment are to stabilize or improve hepatic function and reduce the likelihood of recurrent hepatitis C infection.

Data on preemptive treatment are scarce. A retrospective analysis of outcomes of 26 cirrhotic transplant candidates treated with interferon, with or without ribavirin, reported no recurrent HCV among 6/6 individuals who achieved SVR prior to transplantation, although adverse events were frequent and severe (Alvarez 2003). Preemptive treatment carries significant risks such as serious adverse events and potential acceleration of liver deterioration (see Treatment for Decompensated Cirrhosis section in this chapter), but some individuals may benefit. More research is needed before this approach becomes the standard of care.

The goal of early post-transplant therapy is to avert histological damage from recurrent HCV. Treatment is more effective in individuals with low viral loads. HCV-RNA levels are usually at their lowest immediately after transplantation, before rising to levels up to 20-fold higher than before transplantation (Feray 1994). Singh and colleagues found that early treatment with six months of interferon did delay recurrence of HCV. Recurrence occurred at a median of 408 days after transplantation in the treated group vs. a median of 193 days after transplantation in the untreated controls; P=0.05). Otherwise, no significant differences were observed, either in the frequency of recurrence or the severity of recurrent HCV disease (Singh 1998). Sheiner and colleagues randomized 86 transplant recipients to a regimen of interferon alfa-2b, 3 MIU thrice weekly, or to a control arm who did not receive interferon. Recurrent hepatitis C occurred less frequently in the interferon arm (8 vs. 22; P=0.017). HCV-RNA levels were categorized as low, moderate, or high. In the treated group, high HCV-RNA levels at one and three months were significantly associated with risk of recurrence (risk was 3.1 times greater at month one; P=0.01; at month three, risk was 3.9 times greater; P=0.006). There was no significant difference in actuarial survival between groups at one and two years (Sheiner 1998).

Early treatment with standard interferon plus ribavirin has shown more promising results. Beginning three weeks after transplantation, 36 individuals were given combination therapy for one year. At 36 months after completion of therapy, 33% (12/36) achieved sustained virological and biochemical responses. Progression to severe hepatitis occurred in 11% (4/30) of non-responders (Mazzaferro 2001). Dose reductions due to hemolytic anemia occurred frequently. Terrault and colleagues have treated 25/49 eligible transplant recipients for 48 weeks; 23 have completed treatment and follow-up. Treatment was initiated 1.7–9.3 weeks (median: 5.1 weeks) after transplantation. Participants were randomized to receive an induction/maintenance regimen of standard or pegylated interferon, with or without a gradually escalating dose of ribavirin (400 mg/day to 1.0–1.2 g/day, by body weight). Only 23% received full-dose ribavirin; 84% were able to tolerate full-dose interferon. Overall, only 3/23 achieved SVR; those with undetectable HCV RNA prior to treatment were more likely to achieve SVR (P=0.0009). After completion of treatment, most had mild liver disease; 78% had stage 0 fibrosis, and 72% had ≤ grade-1 disease activity, suggesting histological benefit in the absence of virological response. The discontinuation rate was high: five individuals left before starting treatment, and 19 discontinued due to adverse events. Five deaths occurred during the study, none treatment-related (Terrault 2003). Larger, randomized studies of safety, efficacy, and tolerability of combination therapy for this indication are needed.

The outcome of treatment for recurrent hepatitis C varies, depending on pre-transplant HCV-RNA levels, genotype, regimen, duration of treatment, and an individual's capacity for tolerating treatment. Adverse events requiring dose modifications are common, especially hemolytic anemia due to ribavirin (De Vera 2001; Kornberg 2001; Lavezzo 2002; Narayanan 2002; Samuel 2003). Ribavirin is eliminated by the kidneys. Levels of ribavirin tend to build up when renal function is impaired, and renal impairment is common in liver transplant recipients. Jain and colleagues examined the incidence of hemolysis and renal impairment among transplant recipients on combination therapy. Serum creatinine levels were higher (median of 1.3 mg/dL vs. 1.0 mg/dL), and clearance of creatinine was significantly lower (median 66.47 vs. 96; P=0.018), among those who experienced hemolysis (Jain 2002a).

Table 27. Treatment of Recurrent Hepatitis C: Outcomes/Dose Reductions/Discontinuations

Author	Regimen	Duration	N Participants	% SVR	Histological Outcomes	Dose Reduction	Discont-inuations
Samuel 2003a	IFN 3 MIU 3 x week + RBV 1,000–1,200 mg/day or control group	12 months	N=52 treated: 28 controls: 24	21% (6/28)	No significant improvement in liver histology	Not available	43%
Bizollon 2003	IFN + RBV for 24 weeks, then one year of RBV maintenance therapy	18 months	N=54	24% (13/54) 3 years post TX	For virological responders: improved in 12/14*; 5/14 had normal or nearly normal liver histology	Not available	Not available
Firpi 2002	IFN 3 MIU 3 x week + RBV 800–1,000 mg/day	12 months	N=54	30% (16/54)	For virological responders, no significant progression of liver fibrosis	72%	Not available
Lavezzo 2002	IFN 3 MIU 3 x week + RBV 800 mg/day	6 or 12 months	N=57 6 months: 27 12 months: 30	22% (6/27) 17% (5/30) 1 year post TX	In end-of-treatment responders, decreases of >2 points on the HAI score	51%	Not available
Narayanan 2002	IFN 3 MIU 3 x week + RBV 800–1,000 mg/day	12 months (or more)	N=26	23% (6/26) > 6 months post TX	Decreases of >2 points on the HAI score achieved by 75% of virological responders and 67% of non-responders	66%	50% after 1 year
Nelson 2002	IFN 3 MIU 3 x week + RBV 800–1,000 mg/day	12 months	N=54	30% (16/54) 6 months post TX	In those with SVR, no significant fibrosis progression within 6 months post TX	72%	Not available
Ahmad 2001 (Arm A)	IFN 3 MIU 3 x week for 1 month, then IFN 5 MIU 3 x week for 5 months	6 months	N=20	2.5% (1/20)	No improvement in inflammatory scoring; worsening fibrosis score	Not available	50% (10/20)
Ahmad 2001 (Arm B)	IFN 3 MIU 3 x week + RBV 1,200 mg/day for 1 month, then IFN 5 MIU 3 x week + RBV 1,200 mg/day for 5 months	6 months	N=20	20% (4/20)	No improvement in inflammatory scoring; worsening fibrosis score	Not available	40% (5/20)

* At the end of treatment, 14 of 54 participants (26%) had undetectable HCV RNA; all 14 were followed for a mean interval of three years after completion of treatment.

End-of-treatment results are available from a study of safety, efficacy, and tolerability of pegylated interferon monotherapy in transplant recipients. Vogel and colleagues randomized 65 transplant recipients with recurrent HCV to either 48 weeks of treatment with 180 μg/week of pegylated interferon alfa-2a (33) or no treatment (32). Participants were stratified by high (>1,000,000) or low (<1,000,000) HCV-RNA levels. Week 48 results were available from 49 participants (23 treated and 26 contols). A total of 16 individuals discontinued participation in this study; 10 from the treatment arm and 6 from the control arm.

Table 28. Hepatitis C RNA Levels During Treatment

HCV RNA Level	Week 4	Week 12	Week 24	Week 48
Undetectable	12% (4/33)	33% (11/33)	31% (10/32)	35% (8/23)
2.0-log drop	36% (12/33)	45% (15/33)	50% (16/32)	48% (11/23)

Vogel 2002

During the study, four rejection episodes occurred in the treatment arm; two of these individuals completed the trial. In the treatment arm, 45% (15/33) had at least one serious adverse event. In the control arm, 25% (8/32) had at least one serious adverse event. There were two deaths in the treatment arm (one from hepatic and renal failure and another from pulmonary metatases); neither were considered to be related to treatment (Vogel 2002).

Preliminary data from several ongoing studies of pegylated interferon alfa-2b plus ribavirin are available.

Table 29. Treatment of Recurrent HCV with Pegylated Interferon and Ribavirin

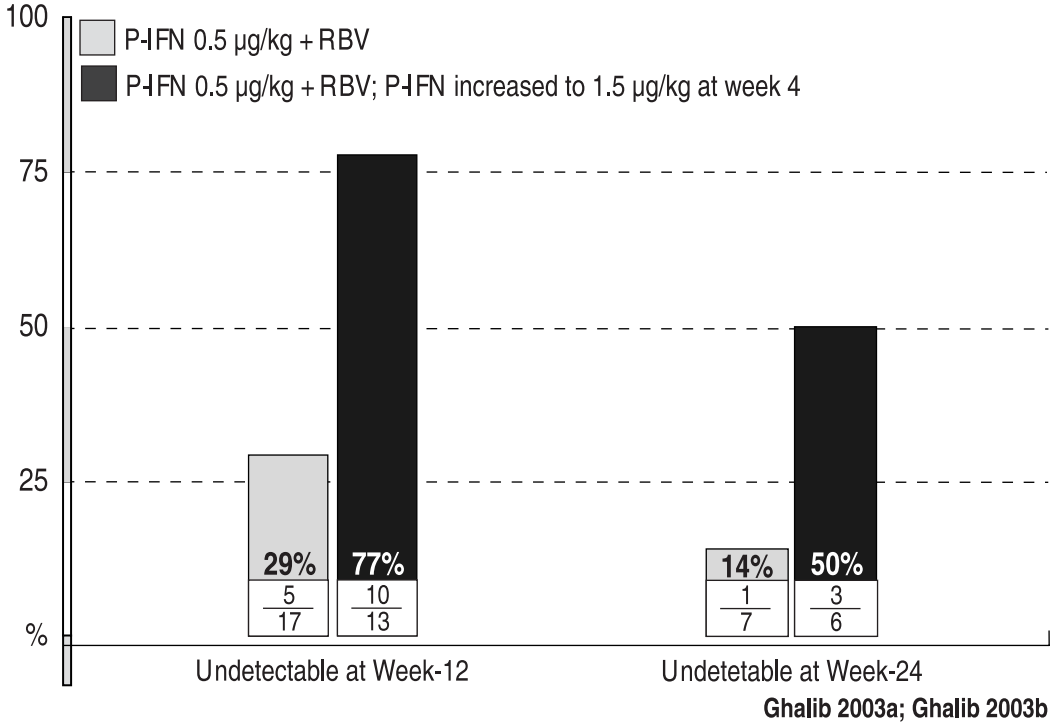
Author	Regimen	Duration	N Participants	% SVR or ETR	Histological Outcomes	Dose Reduction	Discontinuations
Lorenzini 2004	P-IFN alfa-2b 80 µg/week + RBV 600 mg/day	24 weeks; if HCV RNA undetectable, 24 additional weeks	N=18	SVR: 39%	Data not provided	RBV reduced in 10 & discontinued in 2 G-CSF used; no P-IFN dose modifications	3 cirrhotics had to discontinue due to hepatic decompensation
Dumortier 2003	P-IFN alfa-2b, escalated from 0.5 µg/kg to 1.0 µg/kg/week + RBV, escalated from 400 mg to 1,000–1,200 mg/day	12 months	N=20 Genotype 1=16	SVR: 45% (9/20)	Mean decrease of METAVIR score post TX: A 1.8 to A 0.3 F 2.2 to F 1.6	P-IFN: 37% (6/16) RBV: 81% (13/16)	20% (4/20)
Mukherjee 2003	P-IFN alfa-2b 1.5 µg/kg/week + RBV 800 mg/day + folic acid 1 mg/day	Genotype 1 & 4: 12 months Genotype 2 & 3: 6 months	N=39 Genotypes 1&4=34; Genotypes 2&3=5	SVR: 30% (12/39); data pending from 3 people	Fibrosis at ETR: improvement: 33% (6/18) stable: 56% (10/18) worsening: 11% (2/18)	Not Available	44% (17/39)
Lavezzo 2003	P-IFN alfa-2b 1.0 mg/kg/week + RBV 800 mg/day	6 or 12 months	N=16 (treatment-naive)	Not available	Not available; 3 with normal ALT levels at ETR	88% (14/16)	44% (7/16)
Neff 2003a	P-IFN alfa-2b 1.5 mg/kg/week + RBV 400–600 mg/day	Not available	N=32 (non-responders to IFN + RBV)	ETR:18% (6/32)	Not available; biochemical improvement seen in 50% (16/32)	P-IFN: 60% (19/32) RBV: 28% (9/32)	28% (9/32)
Neff 2003b	P-IFN alfa-2b 1.5 mg/kg/week + RBV 400–600 mg/day	At least 24 weeks	N=30 (treatment-naive)	ETR: 27% (8/30)	Not available	P-IFN: 40% (12/30) RBV: 43% (13/30)	None
U. P. Neumann 2003	P-IFN alfa-2b 1–1.5 µg/kg/week + RBV 400–800 mg/day	48 weeks	N=25	SVR: 36% (9/25)	No change in fibrosis or inflammation from baseline to week 72	Doses reduced for side effects neutropenia: 60% (15/25) fever, chills, headache & vertigo: 48% (12/25) anemia: 20% (5/25) psychiatric: 8% (2/25)	None
Samuel 2003b	P-IFN alfa-2b 1 µg/kg/week (mean dose) + RBV 7.5 mg/kg/day (mean dose)	Genotype 1: 12 months Genotype non-1: 6 months	N=22 Genotype 1=17 Genotype non-1=5 treatment-naïve=15 non-responders=6 relapser=1	SVR Overall: 18% (4/22) genotype 1: 13% (2/17) non-1: 40% (2/5) TX-naïve: 26% (4/17) prior TX: 0%	Normal ALT 50% (11/22) 6 months after completion of treatment	P-IFN: 27% (6/22) RBV: 45% (10/22)	63% (14/22) for intolerability: 27% (6/22)* for non-response: 36% (8/22)

* One death was reported; its cause and relationship to treatment were not described.

Serious adverse events occurred frequently across these studies, including severe depression, neutropenia, thrombocytopenia, anemia, acute pancreatitis (N=1; relationship to study treatment not described), organ rejection (N=3; relationship to study treatment not described), jaundice, and severe flulike symptoms. Neff and colleagues reported using multiple therapeutic interventions in one study, where 10% were given blood transfusions, 20% received erythropoietin, 43% were given neupogen, and 43% received treatment for clinical depression (Neff 2003b). Each investigator concluded that efficacy and tolerability were poorer in transplant recipients. Initiation of treatment with lower doses, and gradual dose escalation are current strategies for increasing the efficacy and tolerability of treatment for recurrent hepatitis C in transplant recipients.

Higher doses of pegylated interferon appear to be more effective, based on interim reports of week-12 and week-24 virological responses from 30 transplant recipients treated with two different doses of pegylated interferon alfa-2b (0.5 μg/kg or 1.5 μg/kg) plus 600 mg/day of ribavirin, increased to 800 mg/day at week 4. Growth factors were used to decrease dose reductions, although 18% (3/17) in the high-dose arm and 21% (4/19) in the low-dose arm had reductions of their pegylated interferon doses. Both arms had reductions in ribavirin doses (41% and 37%). No differences in toxicity by pegylated interferon dose have been reported (Ghalib 2003a; Ghalib 2003b).

Figure 26. Week-12 and Week-24 Virological Response by Treatment Arm



Ghalib 2003a; Ghalib 2003b

Hepatitis C Treatment in Kidney Transplant Recipients

Hepatitis C infection is common among individuals with end-stage renal disease (ESRD) on hemodialysis;. Estimates of prevalence in the United States range from 6% to 38% (Zacks 2001). Overall, survival in HCV-positive individuals with ESRD improves with kidney transplantation vs. maintenance with hemodialysis (Fabrizi 2002; Knoll 1997; Siren 2002). Although rapidly progressive hepatitis C appears less frequently in kidney transplantation, long-term follow-up indicates that HCV infection does have an adverse effect on survival, with the risk of graft rejection increasing at five years after transplantation (Fabrizi 2002; Siren 2002). Mathurin and colleagues compared survival at ten years after transplantation between three groups (HBV-infected, HCV-infected and matched, uninfected controls), finding that HCV infection significantly decreased survival (65 ± 5% vs. 80 ± 3% for controls; $P<0.001$). Graft survival at ten years after transplantation was also significantly lower in those with HCV infection (49 ± 5% vs. 63 ± 3% for controls; $P<0.0001$) (Mathurin 1999).

Interferon treatment for HCV in kidney transplant recipients has resulted in episodes of graft rejection (Kakimoto 1994; Rostaing 1996; Takahara 1995). Due to the risk of acute renal failure during treatment, and the frequency of relapse after completion of treatment for HCV, treatment of hepatitis C after kidney transplantation is contraindicated (Pol 2002).

Interferon Monotherapy: Efficacy in Dialysis Recipients before and after Kidney Transplantation

Although promising data on safety and efficacy of interferon monotherapy in dialysis recipients have emerged, tolerability remains a significant consideration. Degos and colleagues planned a multicenter, prospective trial to assess the tolerance and efficacy of interferon in 120 dialysis recipients with HCV. The initial dose of interferon was 3 MIU thrice weekly, with reduction to 1.5 MIU thrice weekly in case of side effects; planned duration of treatment was 48 weeks. By the time 37 individuals had been enrolled in the study, it was prematurely terminated due to the frequency of severe adverse events and discontinuations. Treatment was stopped in 19/37 and life-threatening side effects were recorded in 12 individuals. Dose reductions were necessary in 21 individuals by week 24; only 18 reached the 48th week of treatment. Of these 18, 38% (7/18) achieved SVR (Degos 2001).

Izopet and colleagues treated 23 dialysis recipients with 3 MIU of interferon thrice weekly for either 6 (N=12) or 12 months (N=11). Sustained viral clearance was achieved by 42% (5/12) of those treated for 6 months and 64% (7/11) of those who received 12 months of treatment (Izopet 1997).

Another prospective, controlled study evaluated the outcome of kidney transplantation in 30 individuals with HCV infection awaiting transplantation. A year of interferon monotherapy (3 MIU thrice weekly) was given to 15 individuals; another 15 were untreated. Kidney transplantation was performed in 11/15 who received HCV treatment, and in 10/15 controls. A year after transplantation, HCV RNA was undetectable in 4/11 treated individuals, and liver biopsy was performed on all transplant recipients. Those who had received HCV treatment had significantly lower mean HAI scores than untreated controls (1.82 ± 0.6 vs. 5.5 ± 1.35; $P<0.0001$) (Huraib 2001). In another study of efficacy and tolerance of interferon monotherapy in 19 HCV-infected individuals with renal impairment, treatment was discontinued in 9/19. Of those who completed treatment, 7/10 achieved SVR. Renal transplantation was performed in 10 individuals; 3 of them had undetectable HCV RNA at the time of transplantation, and 2 of the 3 remained virus-free 24 months after transplantation (Campistol 1999).

Combination Therapy

Safety, efficacy, and tolerability of combination therapy for HCV in individuals with kidney dysfunction are significant concerns. Clearance of interferon and ribavirin decreases with renal impairment (Bruchfeld 2002; Pol 2000; Rostaing 1998). Results from a pilot study of combination therapy using lower doses of ribavirin (200–400 mg/day), careful monitoring of hemoglobin levels, and the use of growth factors for anemia as needed, indicate that HCV infection in dialysis recipients may be treated with combination therapy. Further study is necessary (Bruchfeld 2001).

Pegylated Interferon

The safety and efficacy of pegylated interferon in individuals with renal impairment is being assessed in ongoing studies (Fabrizi 2002).

Management of Side Effects and Adverse Events

The side effects of interferon (whether standard or pegylated) and ribavirin are considerable (see adverse events tables from Fried 2002; Lindsay 2001; Reddy, 2001; Zeuzem 2001). The most common side effects of interferon are flulike: fever, headache, chills, muscle aches, and fatigue. Scheduling interferon injection before bedtime (or on Friday nights for once-weekly pegylated interferon) may help to decrease side effects. Muscle aches, headaches, and fever can be treated with acetaminophen or other nonsteroidal anti-inflammatory drugs prior to injection of interferon. Weight loss is common; eating several small light meals daily or larger meals when possible may help. Nausea and anorexia can be managed with antiemetics or marinol. Adequate hydration and light exercise for 30 minutes, at least three times per week, may alleviate fatigue and headaches. Insomnia can be treated with medication if necessary. A thorough knowledge of potential side effects by clinicians and those undergoing treatment is crucial to preparing for treatment of hepatitis C infection.

Some treatment-related adverse events may be life-threatening. A range of severe adverse events have been recorded and are categorized below, with current strategies for their management.

Neuropsychiatric Side Effects

Neuropsychiatric adverse events, such as depression, anxiety, irritability, and insomnia, have been associated with interferon. Depression, irritability, and insomnia were reported by 30–40% of participants in the Peg-Intron®/Rebetol® trial; overall, psychiatric adverse events occurred among 77% of trial participants (Schering package insert, 2001). In studies of Pegasys®, 33–38% of participants reported anxiety, nervousness, or irritability (Roche package insert, 2002). These adverse events are a significant concern, because depression can be a symptom of untreated hepatitis C (see Chapter II, Natural History of Hepatitis C), and many of the high-prevalence populations (such as injection drug users, HIV-positive individuals, and veterans) have a high prevalence of depression and other psychiatric disorders. Careful monitoring during treatment is important.

The most serious neuropsychiatric adverse events are severe depression, suicidal ideation, and suicide attempts. Suicidal behavior (attempts and suicide) has occurred in <1% (Roche) to 2% (Schering) of trial participants (Roche package insert, 2002; Schering package insert, 2001). Treatment with interferon must be discontinued if an episode of severe depression with suicidal ideation occurs. Suicides and attempted suicide have been reported during interferon therapy in individuals with no prior history of mental illness (Fattovich; Janssen 1994; Schering package insert, 2001). One case report of a 50-year-old woman with no significant psychiatric history provides a harrowing illustration of interferon-induced depression. During treatment with interferon, she developed irritability, anxiety, insomnia, and depression; she poured lamp oil on herself and set herself on fire. Fortunately, she survived (Fukunishi 1998). Severe interferon-related depression

may not always disappear after treatment discontinuation. In one study, prevalence of suicide attempts among 306 individuals during and after interferon therapy increased from 0% (during therapy) to 1.3% in the six months after therapy (Rifflet 1998).

Clinical trials have used different instruments to assess depression, or have relied upon self-reporting of depression, which may not reflect the true incidence of depression among those on treatment (estimated at 20–30%) (Fried 2002b). It may be difficult for people on HCV treatment and their clinicians to distinguish clinical depression from other common side effects from interferon (such as insomnia and fatigue). Although there is no specifically validated instrument to assess interferon-related depression, different instruments have been used to measure interferon-induced depression. The Montgomery-Asberg Depression Rating Scale (MADRS) was used in a small (N=33) prospective evaluation of the incidence of, and predictive factors for, depression prior to starting interferon. Participants with a high baseline MADRS (≥ 3) had more intense depressive symptoms than those with low baseline scores (<3) (Castéra 2002). Another group used the Minnesota Multiphasic Personality Inventory (MMPI) at baseline and three months after initiation of interferon to identify individuals at risk for depression. Three months after initiation of interferon, 64% (9/14) of those with a baseline score of ≥ 60/100 developed a depressive mood, and 11% (5/44) with baseline scores <60/100 showed medium-level depression after three months on treatment (Scalori 2000).

Sanchez and colleagues used the Beck Depression Inventory (BDI) to predict and identify HCV-treatment-related depression in a study of 76 individuals from three HCV treatment trials. Depression increased significantly during HCV treatment, regardless of the regimen used (P≤ 0.001). The severity of treatment-induced depression correlated with the baseline BDI score (P≤ 0.001). Individuals with severe depression had a greater incidence of early withdrawal from treatment trials than those with no, or mild-to-moderate depression (34% vs. 11% and 15% respectively). Those with severe depression who continued treatment had lower rates of week-12 viral response than did those with mild-to-moderate depression (34% vs. 62%) (N. Sanchez 2002).

When mild-to-moderate interferon-induced depression is identified, it can often be managed, thus improving quality of life and, possibly, treatment adherence and outcomes. Because they appear to be safe and easily tolerated in individuals with liver disease, selective serotonin reuptake inhibitor (SSRI) antidepressants are often used to treat interferon-induced depression (Gleason 2002; Hauser 2002: Krauss 2002; Schramm 2000).

Some individuals and their clinicians may choose to start preemptive treatment for depression before the initiation of interferon. Schafer and colleagues evaluated the effect of pre-treatment with citalopram (an SSRI) among 25 methadone recipients with psychiatric histories. Episodes of major depression were significantly less frequent during four months of HCV treatment in the citalopram group than in those who were not pre-treated (14% vs. 64%; P=0.028) (Schafer 2003b).

Careful assessment of baseline depression and an ongoing screening process during therapy should be a routine part of HCV treatment. Exploration of the pathophysiology of interferon-induced depression is needed, so that better interventions may be developed.

Although uncommon, other severe, interferon-induced neuropsychiatric adverse events have been reported, including acute psychosis, confusion and coma, memory loss, neuropathy, panic attacks

and personality changes, and seizures in persons with and without a history of such disorders (Ahmed 2003a; Anton 2000; Fried 2002b; Hosoda 2000; Kanno 1999; Schafer 2000; Shakil 1996).

Sensory Adverse Events

Interferon-related adverse events may affect hearing and vision. Tinnitus (ringing or roaring noises) and hearing loss are rare, usually reversible side effects of interferon. Ocular pathologies, such as blocked blood supply to the retina, retinal hemorrhage, and cotton wool spots are known side effects of standard interferon (Fried 2002b; Kadayifclar 1999; Norcia 1999). The effect appears to be dose-dependent, with reported incidences across different studies ranging from 18% to 85% (Hayasaka 1998). In some instances, interferon may need to be discontinued to prevent permanent damage.

Pegylated interferon-based therapy has been linked with serious ophthalmologic side effects. Ahmed and colleagues reported serious ophthalmic adverse events in 20/4800 people who received at least one dose of pegylated interferon alfa-2b and fixed or weight-based dosing of ribavirin. Ophthalmic damage was diagnosed in 16; 1 needed surgery for a detached retina. Treatment was discontinued in 17/20; 3 had persistent symptoms after treatment discontinuation (Ahmed 2003b).

Assessment of ocular problems at baseline, and regular monitoring, including color vision testing, are recommended.

Autoimmune Disorders and Adverse Events

Extrahepatic manifestations of untreated hepatitis C may appear as immunologic disorders (see Chapter II, Natural History of Hepatitis C). Autoimmune disorders may be induced or worsened during interferon therapy. Interferon therapy may be contraindicated for individuals with preexisting autoimmune hepatitis or thyroid disease, depending in part on the severity of the condition, because it can exacerbate these disorders (Dumoulin 1999; Heller 1996). Interferon has been associated with rare instances of celiac disease (damage to the intestinal mucosa caused by an immune response), inflammatory bowel disease, autoimmune hepatitis, induction of autoantibodies (antibodies that attack parts of the tissues in a person's own body), psoriasis, sarcoidosis (chronically inflamed tissue; formation of nodules in the lymph nodes, bones and skin), myasthenia gravis (progressive muscle weakness), type 1 diabetes mellitus, thrombocytopenia purpura (platelet destruction), and lupus-like syndrome (Bell 1999; Fattovich 1996; Fried 2002b; Leveque 2001; Nawras 2002; Neglia 2001; Papo 2002; Tada 1996; C. Taylor 2000; Wolfer 1996; Zuffa 1996).

Cardiac Adverse Events

A range of rare cardiac adverse events from interferon and ribavirin has been reported, from arrhythmias to acute congestive heart failure (Fried 2002b). Interferon and ribavirin are contraindicated for individuals with a history of significant or unstable cardiac disease. During treatment with interferon and ribavirin, close monitoring of individuals with a history of cardiovascular disease (heart attack, arrhythmia) is recommended.

Hematologic Toxicities

Interferons are known bone marrow suppressants, causing significant decreases in white blood cell counts, hemoglobin, and platelet counts (Peck-Radosavljevic 2002; Wong 1996). The adverse events induced by pegylated interferons are similar to those from standard interferons, with the exception of an increased frequency of hematologic toxicities (neutropenia, a decrease in white blood cells called neutrophils, which resolves after discontinuation or completion of therapy; and thrombocytopenia, a decrease in platelets). Ribavirin is associated with reversible hemolytic anemia and it may exacerbate interferon-induced neutropenia (Bodenheimer 1997; De Franceschi 2000; Dusheiko 1996; Schering package insert, 2001). In rare instances, interferon induces aplastic anemia (Schering package insert, 2001; Roche package insert, 2002).

Data from chemotherapy recipients have been used to evaluate the risk of infection from interferon-induced neutropenia. Low neutrophil counts have been a criterion for exclusion in many HCV treatment trials, and used as triggers for dose reductions of interferon, both in clinical trials and clinical practice. Individuals with chronic hepatitis C, however, may not be at the same risk for infections as immunosuppressed chemotherapy recipients, with the possible exceptions of cirrhotics and coinfected persons. A retrospective analysis of data from 119 persons treated for HCV with interferon and ribavirin found that no bacterial infections occurred in neutropenic individuals during treatment (Soza 2002). Additionally, Blacks have significantly lower neutrophil counts than Whites (Freedman 1997; Reed 1991; Zezulka 1987). Soza and colleagues have estimated that there may be 76,000 black Americans with HCV and constitutional neutropenia. Using a universal neutrophil cutoff for hepatitis C treatment trials may result in the exclusion of many black volunteers. Research to identify an appropriate neutrophil threshold for Blacks, and a safe threshold for triggering dose reductions is needed.

Dose reduction is the standard of care for interferon-induced neutropenia, yet suboptimal dosing of interferon may impair treatment outcomes. Maintaining doses of at least 80% of both drugs, for at least 80% of the course of therapy, increases the likelihood of achieving an SVR (McHutchison 2002). Hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) can be used to boost neutrophil counts. Clinical trials of G-CSF as a therapy for hepatitis C, either alone or with interferon, have demonstrated safety, but not antiviral efficacy (Carreno 1996; Carreno 2000; Schiffman 1998). It is not current clinical practice to use G-CSF for neutrophil rescue therapy during hepatitis C treatment. More information is needed to determine if G-CSF rescue therapy is a viable option.

Thrombocytopenia (low platelets) may be a manifestation of untreated hepatitis C itself, especially among cirrhotics and those with advanced liver damage, or may be induced by interferon therapy (Giannini 2002; Pockros 2002; Ramos-Casals 2003). Interferon has been used as a treatment for the thrombocytopenia caused by HCV, and platelet counts have increased after therapy (Benci 2003; Rajan 2001). If platelet counts drop markedly during therapy with pegylated interferon, dosing may need to be modified or treatment discontinued, as there is growing concern among clinicians about spontaneous intracranial bleeding in patients with fewer than 50,000 platelets/mm^3.

Hemolytic anemia (destruction of red blood cells) is a common, usually reversible side effect of

ribavirin. Dose reduction is one strategy used for management of ribavirin-induced anemia, but suboptimal dosing may result. Epoetin-alfa, a genetically engineered version of erythropoietin (EPO), a human protein that stimulates production of red blood cells, has been used to maintain or restore full doses of ribavirin, resulting in significantly higher hemoglobin levels (Dieterich 2001; Dieterich 2002; Gergely 2002; Senkbeil 2003; Wasserman 2000; Weisz 1998). When ribavirin is used with pegylated interferon, the recovery period from treatment-induced anemia may be longer than that observed with ribavirin and standard interferon; use of epoetin-alfa may contribute to recovery (Azzam 2003).

Menstrual Irregularities

Menstrual irregularities—amenorrhea or prolonged menstruation—have been reported in female cynomolgus monkeys given pegylated interferon alfa-2a every other day for one month, at a dose approximately 180 times that recommended for a 60-kg person. Menstrual irregularities were accompanied by a decrease and a delay in the peak levels of two hormones, 17ß estradiol and progresterone. When the dose was lowered to approximately 30 times the weekly recommended dose, no effect on the duration of menstruation or on estradiol and progesterone levels was observed. After treatment was discontinued, normal menstrual rhythm returned. According to the label, pegylated interferon alfa-2a may impair fertility (Roche package insert 2002).

Care During Treatment

Preliminary data from a randomized, controlled study suggest that a multidisciplinary approach to providing care during hepatitis C treatment decreases the number of discontinuations and increases quality of life during the first three months of therapy. One of two models, standard of care (involving routine supportive care from a gastroenterologist or hepatologist) or an active intervention (involving patient education, regular, scheduled telephone consultations with experienced nurses, aggressive side effects management, and behavioral therapy) were provided to 67 individuals from 9 different medical practices during the first 12 weeks of HCV treatment. Both groups were monitored for frequency of adverse events, and a week-12 assessment of quality of life was performed. At week 12, 4/39 (10%) of the standard of care group had discontinued treatment vs. 1/38 (3%) of the active intervention group. Members of the active intervention group reported higher quality of life scores in all domains, with the exception of bodily pain and mental health (Flamm 2002).

Hepatitis C Treatment in Other Understudied Populations

People with Hemophilia

People with hemophilia have been excluded from pivotal treatment trials, mainly because of the risk of biopsy on people with coagulation disorders. Data on interferon with and without ribavirin in hemophiliacs come from small studies. Information about safety and efficacy of pegylated interferon, with and without ribavirin, is not yet available in this population.

Table 30. HCV Treatment Outcomes for Hemophiliacs

Author	Regimen	Duration	N Participants	% SVR	Biochemical Improvement	Discontinuations
Hanley 1996	IFN alfa-2a 3 MIU, 3 x week	24 weeks	N=31	24% (7/31)	28% (8/31) sustained normal ALT	Not available
Rumi 1997	IFN alfa-2b 3MIU, 3 x week	12 months*	N=101 Treated: 50 Controls: 51	13% (6/45) SVR + sustained normal ALT	13% (6/45) SVR + sustained normal ALT	Treated: 5/50 Controls: 1/51
Shields 2000	IFN alfa-2b 3MIU, 3 x week + RBV 1–1.2 g/day	48 weeks	N=28	71% (20/28) 16-month mediam follow-up	Not available	11/28 (3 of 4 who discontinued TX early achieved SVR)
Sauleda 2000	IFN + RBV	12 months	N=20	35% (7/20)	Not available	0%
Fried 2002c	3 Arms (see below)	48 weeks	Total N=113 Adolescents: 37 Adults: 76	Adolescents: 59% Adults: 15%	Not available	14% (16/113)
	IFN alfa-2b 3 MIU, 3 x week + RBV 1,000 mg/day	48 weeks	N=56	29% (16/56)		
	IFN monotherapy	48 weeks	N=14	7% (4/57)		
	IFN monotherapy for first 12 weeks, then IFN + RBV for 36 weeks	48 weeks	N=43			
Franchini 2002	IFN alfa-2b 5 MIU, 3 x week + RBV 1–1.2 g/day	12 months	N=33 (IFN non-responders)	33% (11/33)	42% (14/33) normal ALT levels at the end of TX	12% (4/31)

*Biochemical non-responders or those with persistently detectable HCV RNA discontinued treatment at week 24.

Children

In the United States, between 68,000 and 102,000 children are chronically infected with hepatitis C (Jonas 2002). Hepatitis C appears to run a more benign course in children than it does in adults (Guido 1998; Kage 1997; Vogt 1999); however, hepatitis C is not invariably less severe in children. Badizadegan and colleagues examined liver biopsy specimens from 40 children (age range: 2–18.6), finding significant fibrosis in 58% (23/40) and cirrhosis in 8% (3/40). In this study, the average duration of infection was 6.8 years (Badizadegan 1998). Fibrosis progression may be a function of duration of infection and aging, as the severity of liver damage increases with adolescence and young adulthood (Jara 2003); therefore, hepatitis C treatment during childhood may present an opportunity to avert progressive disease.

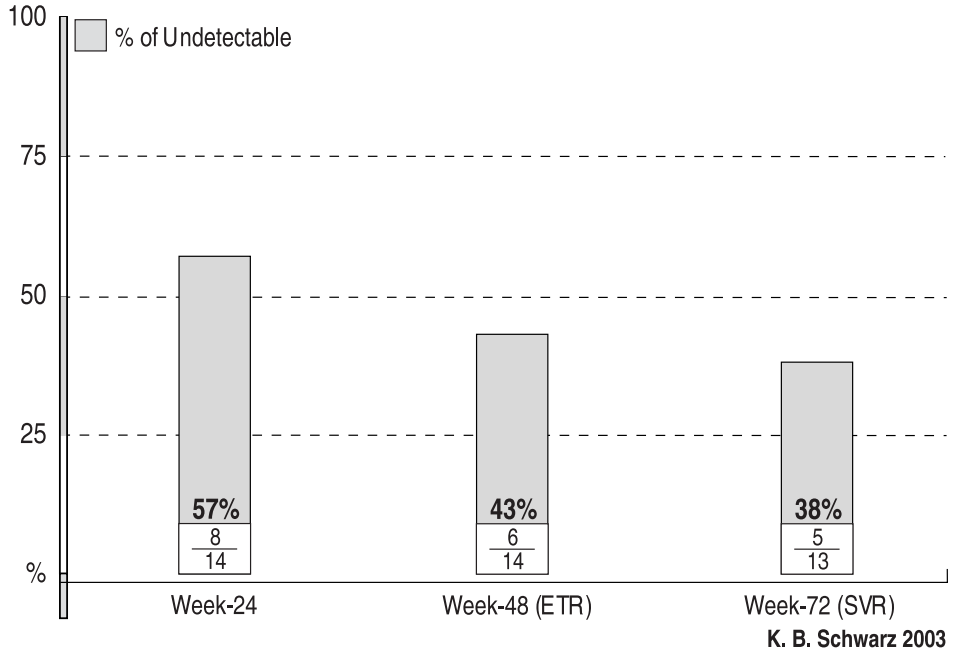
There have not been any randomized, controlled trials of the safety, efficacy, and tolerability of HCV treatment in children, although data from several small studies of interferon monotherapy

have yielded SVR rates ranging from 33% to 50% (Bortolotti 1995; Jonas 1998; Marcellini 1997; Nakashima 2003; A. Sawada 1998; Yuce 2000). Wirth and colleagues conducted an uncontrolled pilot study of efficacy and tolerability of 3 or 5 MIU of interferon thrice weekly plus ribavirin (15 mg/kg per day) in 41 children. Those with detectable HCV RNA after six months of treatment discontinued. When HCV RNA was undetectable at week 24, treatment continued for another 24 weeks. One child discontinued treatment because of severe anemia, and 12 discontinued due to week-24 non-response. Of the 25 children who completed treatment without virological breakthrough, all achieved SVR; the overall SVR rate was 61% (25/41). The rate of SVR in children with genotype 1 was 53% (18/34); all children with non-1 genotypes achieved SVR (Wirth 2002). Two other studies of interferon plus ribavirin in children have yielded sustained virological response rates of 41–45% (Kelly 2001; Süoglu 2002).

Wirth and colleagues reported that children were better able to tolerate combination therapy than adults, although all of them experienced flulike symptoms during the first weeks of treatment. Thyroid autoantibodies developed in 21% (6/28) after six months of treatment, and 11% (3/28) had markedly increased levels of thyroid-stimulating hormone. Dry skin and hair loss developed in three children. All side effects resolved after treatment was ended (Wirth 2002).

Encouraging data on safety and efficacy of pegylated interferon alfa-2a monotherapy in children have been reported from a multicenter, open-label study. The 14 participants were given 180 μg/kg once weekly for 48 weeks.

Figure 27. Virological Response to Pegylated Interferon Monotherapy at Weeks 24, 48, and 72



No serious adverse events were reported; the adverse events most frequently reported—fever, headache, vomiting, appetite loss, and abdominal pain—were described as "mild in intensity." There were four withdrawals from this study: one for week-24 virological non-response, two from elevations in liver enzymes, and one from an exacerbation of preexisting hypertriglyceridemia (K. B. Schwarz 2003).

Wirth and colleagues have reported interim results from an open-label pilot study of a 12-month course of pegylated interferon alfa-2b (1.5 μg/kg) plus ribavirin (15 mg/kg per day) in 52 children and adolescents (mean age: 11.3 years; range: 2–17). Treatment was discontinued at week 24 if HCV RNA was detectable. Of the 46 participants with six month follow-up data, 61% (28/46) achieved SVR. All participants with non-1 genotypes achieved SVR; 52.6% (20/38) with genotype 1 achieved SVR. The remaining 39% (18/46) were primary non-responders, relapsers, and one treatment discontinuation for side effects. No serious adverse events were reported; treatment was characterized as "well tolerated" (Wirth 2003).

More study of pegylated interferon, with and without ribavirin, is needed in pediatric populations.

HCV Treatment and Care for Individuals with Psychiatric Disorders, Active Drug and/or Alcohol Users, and the Dually Diagnosed

> *Treatment of HCV infections should not be withheld from patient populations with complicated social problems.*
>
> —G. Robaeys
> *Acta Gastroenterology*

Revised Indications for Active Drug Use

Until 2002, active drug use was regarded as a contraindication for treatment with interferon. Thankfully, the NIH Consensus Panel revised its guidance in the 2002 Statement, which reads:

> Many patients with chronic hepatitis C have been ineligible for trials because of injection drug use, significant alcohol use, age, and a number of co-morbid medical and neuropsychiatric conditions. Efforts should be made to increase the availability of the best current treatments to these patients. Recent, albeit limited, experience has demonstrated the feasibility and effectiveness of treating chronic hepatitis C in people who use illicit injection drugs, known as injection drug users (IDUs). This is potentially important because injection drug use is the most common risk factor for new HCV infections in the United States, and successful treatment may reduce transmission. Management of HCV-infected IDUs is enhanced by linking these patients to drug treatment programs. Treatment for drug and alcohol abuse should be made available to all patients who want and need it. Access to methadone treatment programs should be fostered for HCV-infected IDUs whether or not they are receiving treatment for HCV. Methadone treatment has been shown to reduce risky behaviors that can spread HCV infection, and it is not a contraindication to HCV treatment. Efforts should be made to promote collaboration between experts in HCV and healthcare providers specializing in substance-abuse treatment. HCV therapy has been successful even when the patients have not abstained from continued drug or alcohol use or are on daily methadone. However, few data are available on HCV treatment in active IDUs who are not in drug treatment programs. Thus, it is recommended that treatment of active injection drug use be considered on a case-by-case basis, and that active injection drug use in and of itself not be used to exclude such patients from antiviral therapy.

Hepatitis C Treatment in Psychiatric Risk Groups and Active and Recovering Drug and Alcohol Users: The Value of Multidisciplinary Care

Clinicians approach these patients from a perspective reflecting their respective training and background. Medical clinicians typically address the toxic effects (such as seizures or alcoholic cirrhosis) of a particular substance or the health consequences of a high-risk lifestyle (such as infectious hepatitis or HIV infection). Psychiatrists and other mental health clinicians focus on the mental health issues prevalent among substance-dependent patients. Chemical dependency counselors typically focus on the individual's destructive preoccupation with obtaining and consuming a psychoactive chemical substance and the negative consequences thereof. For the patient, the issues from all of these perspectives are pressing, often inseparable problems, yet health care providers operate in separate systems of care. The shortcoming of these parallel approaches is that the patient's problems are interrelated and require input from all systems for optimal treatment.

—J. H. Samet
Archives of Internal Medicine

Providing opportunities for hepatitis C care and treatment in populations for which it was formerly contraindicated is complicated. Encouraging results have emerged from different studies of active drug users and individuals with dual diagnoses (mental illness and addiction), as well as those on methadone maintenance. All speak to the need for patient-centered, multidisciplinary care.

Schafer and colleagues found no rationale for continued contraindications to interferon therapy if psychiatric evaluation and multidisciplinary care are provided before and during interferon therapy. They prospectively assessed efficacy, psychiatric side effects, and adherence to hepatitis C treatment (standard interferon 3 MIU, thrice weekly, plus ribavirin 1,000–1,200 mg/day; duration according to genotype and week-24 response) in four groups: individuals with a history of psychiatric disorders; individuals receiving methadone maintenance; former injection drug users; and controls (no past or present psychiatric disorders or drug use). Preexisting and interferon-induced depression did not have a significant impact on the dropout rate or treatment outcomes.

All participants were seen by a psychiatrist twice weekly during their first eight weeks on interferon, and on a monthly basis thereafter. Although five individuals were admitted to the psychiatric ward, not one of these admissions could be directly linked with interferon. Suicidal thoughts were reported in 4–6% of participants, and two individuals dropped out for this reason. In every instance, suicidal thoughts vanished during psychiatric care. Overall, 16% (13/81) developed new depression during treatment and were treated with antidepressants. Six individuals (four with a history of addiction and two from the methadone group) were treated for alcohol abuse during the study; only one of these individuals dropped out of the study (Schafer 2003a).

Table 31. SVR, Adherence, Discontinuation, Depression, and Suicidal Thoughts

	All (N=81)	Control (N=23)	Psychiatric (N=16)	Methadone (N=21)	Former Addiction (N=21)
SVR	37% (30/81)	35% (8/23)	38% (6/16)	48% (10/21)	28% (6/21)
Nonadherence	13% (10/81)	9% (2/23)	6% (1/16)	14% (3/21)	13% (3/21)
Discontinuation	22% (18/81)	13% (3/23)	18% (3/16)	14% (3/21)	43% (9/21)
Mild depression	15% (11/81)	4% (1/23)	25% (4/16)	14% (3/21)	14% (3/21)
Moderate depression	7% (6/81)	4% (1/23)	6% (1/16)	10% (2/21)	10% (2/21)
Severe depression	5% (4/81)	4% (1/23)	13% (2/16)	0%	5% (1/21)
Antidepressants given	16% (13/81)	4% (1/23)	62% (10/16)	24% (5/21)	10% (2/21)
Suicidal thoughts	5% (4/81)	4% (1/23)	6% (1/16)	5% (1/21)	5% (1/21)

Schafer 2003a

Veterans with HCV

El-Serag and colleagues examined the occurrence of psychiatric disorders, and drug and/or alcohol addiction among veterans with hepatitis C who received inpatient care at a VA facility between 1992 and 1999. Of the 33,824 veterans with hepatitis C, 86% had at least one prior or current psychiatric, drug, or alcohol disorder. After controlling for age, sex, and ethnicity, drug and alcohol use, depression, post-traumatic stress disorder, and anxiety were significantly associated with hepatitis C infection (El-Serag 2002).

Despite the significant prevalence of these co-morbidities among veterans with hepatitis C, treatment for hepatitis C using a multidisciplinary model has produced encouraging results. A team of providers, including a hepatologist, psychiatrist, pharmacologist, and nurses, assessed prevalence of co-morbid behavioral emotional disorders (BED) in veterans with hepatitis C at the Cincinnati VA Medical Center. Over 95% had experienced or been diagnosed with a BED (67% had one or more disorders, and 89% had been diagnosed with drug or alcohol addiction). At the time of publication, 90% (83/92) had completed six months of treatment; 50% (47/92) had completed the entire course of therapy and 28% (26/92) remained on treatment. Withdrawals and dropouts (29%) were attributed to personal problems (9%), psychiatric adverse events (7%), disappearance due to suspected drug/alcohol relapse (6%), medical adverse events (5%), and known drug/alcohol relapse (2%). Overall, 20% achieved sustained virological responses, with the highest rate of SVR seen in white males (42%) (Goldsmith 2002).

Nguyen and colleagues looked at the medical records of 206 veterans with hepatitis C who received care at a multidisciplinary medical and psychiatric chronic hepatitis clinic. Psychiatric disorders and/or drug/alcohol addiction were prevalent; 89% had been diagnosed with one or both. Treatment was not given to individuals with minimal liver fibrosis or persons with worsening medical, psychiatric, or drug/alcohol problems. Of the 206, 145 (71%) were treated for hepatitis C with interferon or interferon plus ribavirin. Sustained virological responses were within expected parameters: 16% of those on interferon monotherapy, and 28% of those on interferon plus ribavirin (H. A. Nguyen 2002).

HCV Treatment in Active Injection Drug Users

In the United States, an estimated 3,372,000 individuals have injected drugs (National Household Survey on Drug Abuse, 2000 and 2001). Hepatitis C is highly prevalent among injection drug users; an estimated 70–90% have been infected (M. J. Alter 1998; Donahue 1991; Garfein 1996; Thomas 1995a). Although injection drug users comprise the majority of those infected with hepatitis C, little is known about the safety, efficacy, and tolerability of hepatitis C treatment in this population; until recently, hepatitis C treatment was withheld from active users until they had completed a six-month period of abstinence from drugs and alcohol.

Backmund and colleagues studied the feasibility of initiating hepatitis C treatment during inpatient detoxification treatment. HCV treatment was not withheld or discontinued if relapse to injection drug use occurred during the study. Fifty individuals enrolled in the study. Hepatitis C treatment was initiated two weeks before discharge. After discharge, participants either attended a weekly outpatient program or were sent to an inpatient clinic. Relapse to active drug use occurred in 80% of study participants; 30% began replacement therapy with methadone or dihydrocodeine.

After 12 weeks of treatment, 54% discontinued (10% due to side effects, 10% because of non-adherence and 34% because of virological non-response). Week-12 responders to interferon monotherapy continued treatment for another 36 weeks. The duration of combination therapy was assigned according to genotype: 24 weeks for genotypes 2 and 3, and 48 weeks for genotype 1. Overall, 36% achieved a sustained virological response to treatment (Backmund 2001). This rate of response is within the range from two pivotal clinical trials of interferon monotherapy and combination therapy in non–drug users, although baseline characteristics were different in these trials.

Table 32. SVR After Treatment with Combination Therapy or Interferon: Data from Two Large Clinical Trials

Author	Regimen	Duration	% SVR, Overall
McHutchison 1998	IFN alfa-2b monotherapy	48 weeks	13% (29/255)
McHutchison 1998	IFN alfa-2b + RBV 1,000–1,200 mg/day	24 weeks	31% (70/228)
McHutchison 1998	IFN alfa-2b + RBV 1,000–1,200 mg/day	48 weeks	38% (87/228)
Poynard 1998	IFN alfa-2b + placebo	48 weeks	19% (53/278)
Poynard 1998	IFN alfa-2b + RBV 1,000–1,200 mg/day	24 weeks	35% (96/277)
Poynard 1998	IFN alfa-2b + RBV 1,000–1,200 mg/day	48 weeks	43% (118/277)

Schafer 2003a

Table 33. SVR in Current/Former IDUs by Regimen, Setting, Appointment Attendance, and Baseline Characteristics

Variable	% SVR
Regimen:	
IFN monotherapy	35% (12/34)
IFN + RBV*	38% (6/16)
Setting:	
Inpatient program	20% (1/5)
Home	60% (3/5)
Post-relapse substitution program	53% (8/15)
Relapse to heroin injection	24% (6/25)
Appointment attendance:	
Less than 2/3	6% (1/12)
More than 2/3	45% (17/38)
Baseline Characteristics:	
Genotype 1	26% (7/27)
Genotype 2 or 3	48% (11/23)
HCV RNA <300,000 copies	38% (9/24)
HCV RNA >300,000 copies	35% (9/26)
<29 years old	37% (10/27)
>29 years old	35% (8/23)
Female	41% (7/17)
Male	33% (11/33)

Backmund 2001

*After October 1998, all participants received combination therapy.

Reinfection with HCV

Reinfection with hepatitis C may occur in injection drug users after spontaneous viral clearance of acute infection or sustained virological response to treatment (Dalgard 2002; Proust 2000). The frequency of re-infection is unknown. Backmund and colleagues assessed HCV RNA at 12 and 24 weeks after completion of treatment. Although 56% (10/18) of the cohort had injected heroin (for a range of 4–140 days), none became reinfected during this period. The investigators planned to continue follow-up for one or two more years (Backmund 2001). Dalgard and colleagues followed a group of 27 injection drug users and 18 non-injecting controls who had been successfully treated for hepatitis C five years earlier. Every participant was tested for HCV RNA and underwent a risk assessment. Although 33% (9/27) had injected drugs since completion of therapy, only one individual had detectable RNA at follow-up. Genotypic testing revealed a new infection with genotype 1a (rather than the previous genotype 1b infection).

HCV Treatment in Individuals on Methadone Maintenance Therapy

Hepatitis C infection is common among methadone maintenance recipients. Prevalence estimates range from 67% to 87% (Piccolo 2002; Stein 2001). Psychiatric co-morbidities are prevalent as well, with estimates ranging from 47% to 76% (Brooner 1997; Callaly 2001). Methadone maintenance programs have been successful venues for directly observed therapy with highly active antiretroviral therapy (HAART) and isoniazid (Batki 2002; Clarke 2002; McCance-Katz 2002). Three studies examined safety, tolerability, and efficacy of HCV treatment for individuals on methadone maintenance.

Interim data from the Organization to Achieve Solutions in Substance Abuse (OASIS) reported that 54% achieved an ETR after a six or twelve month course of interferon and ribavirin. A subset of 59/105 achieved SVR (Sylvestre 2002a).

Table 34. Sustained Virological Response Rates from 59/105 Study Participants*

Participant Characteristics	% SVR
Overall	28%
Treatment discontinuation	24%
Pre-treatment psychiatric diagnosis	22%
No prior psychiatric diagnosis	37%
Antidepressant use before therapy	50%
Antidepressant use during therapy	88%
Alcohol consumption during therapy (21% overall)	25%
No alcohol consumption during therapy	29%
>6 months pre-treatment sobriety	37%
<6 months pre-treatment sobriety	30%
No pre-treatment sobriety	17%
Active drug use during treatment (35% overall)	20%
Infrequent drug use during treatment	20–29%
Frequent drug use during treatment	0%

Sylvestre 2002b

*Data on the remaining participants will be available at completion of study.

HCV treatment is feasible for recent drug users, and methadone maintenance may support adherence to treatment. Van Thiel and colleagues treated 120 recent drug users, 52 on methadone maintenance. Their baseline characteristics, preclinical parameters and treatment outcomes were compared to those of 120 non-drug using controls. Discontinuation rates were astonishingly low, despite a grueling regimen of 5 MIU of interferon daily for a minimum of one year (virological responders were continued on therapy until their HCV RNA was undetectable for fifteen consecutive months). Only 15% (18/120) of drug users discontinued (vs. 7% [112/120]) of the control group). Sustained virological response rates did not differ significantly between drug and methadone users (33%) and controls (37%). Access to methadone during this study may have

increased adherence to treatment, because some participants initiated methadone maintenance as a side effects management strategy. Methadone dosing remained stable or increased by 10–15% (Van Thiel 2003).

Two other studies demonstrated the safety, feasibility, and efficacy of providing HCV treatment with methadone maintenance. Buggisch and colleagues retrospectively analyzed data from 39 individuals on methadone maintenance who were treated for HCV with standard interferon plus ribavirin. Participants had to be drug-free (with the exception of methadone) for six months before enrolling. The SVR rate was 46% (18/39)—comparable to that seen in non-methadone-using populations (Fried 2002a; McHutchison 1998; Poynard 1998). Many participants had genotype 2 or 3 (31% or 12/39), and SVR occurred more frequently among these individuals (75% vs. 33% for genotype 1) contributing to the overall SVR rate. There were four discontinuations, two each for side effects and relapse to active drug use (Buggisch 2002). Mauss and colleagues compared HCV treatment outcomes between 50 individuals using methadone maintenance and 50 matched controls. Participants received pegylated interferon plus ribavirin according to genotype. The end-of-treatment response rate in the control arm was 74% (37/50) vs. 50% (25/50) in the methadone arm. In the control group, 54% (27/50) achieved SVR vs. 39% (19/49) in the methadone group. Discontinuation rates for side effects or lack of adherence were 18% (8/45) in the control arm vs. 42% (18/43) in the methadone arm. Most of the discontinuations in the methadone arm occurred before week eight. There was no significant difference in the response rates for those who remained on treatment after week eight; 50% (19/38) of methadone users achieved SVR, as did 56% (27/48) of the control arm. No serious psychiatric side effects were reported in either arm. No information was provided about care and ancillary psychiatric services available to study participants (Mauss 2003a; Mauss 2003b).

The pharmacokinetics of methadone and pegylated interferon alfa-2a (180 μg/week) were evaluated in 24 individuals receiving concomitant methadone maintenance. Baseline levels of methadone were compared with serum samples after single (week 1) and multiple doses (week 4) of pegylated interferon, and pegylated interferon levels were compared with historical data from non-methadone users. The levels of pegylated interferon at week 1 and week 4 were similar to levels in non-methadone users, and methadone levels were similar at baseline and at week 4. No signs of opioid withdrawal were observed. The most frequently reported adverse events—headache, myalgia, fever, fatigue, and appetite loss—were mild or moderate (Sulkowski 2003a).

HCV Treatment and Alcohol Use

Alcohol consumption of over 50 g/day (equivalent to four or five glasses of wine) during HCV treatment decreases the efficacy of antiviral therapy (Ohnishi 1996; Okazaki 1994; Peters 2002). Several factors may contribute to the poorer response to treatment seen in alcohol users. Heavy alcohol intake (>70 g/day) increases HCV quasispecies complexity, which may make HCV less responsive to interferon (Sherman 1999). Alcohol may increase HCV replication; some studies have found higher levels of HCV RNA in alcohol users while others have not observed significant differences between drinkers and nondrinkers (Cromie 1996; Khan 2000; Oshita 1994; Pessione 1998; M. Sawada 1993; Wiley 1998).

A case-controlled study evaluated the effect of different amounts of alcohol on treatment efficacy

in 65 individuals. Alcohol use per day was categorized into four groups: none, ≤ 40 g/day, 41–80 g/day, and >80 g/day. HCV-RNA levels were significantly higher in drinkers, with the heaviest drinkers having the highest titers of HCV RNA. Response to treatment decreased with heavier alcohol intake. Fewer than 5% of those reporting alcohol use of any amount achieved SVR, and non-response to treatment occurred at a significantly greater rate among drinkers (63.1% vs. 10.7%; P<0.001) (Loguercio 2000).

Specific information about the effect of light-to-moderate alcohol intake (<20 g/day) on HCV treatment efficacy is unavailable. Decreasing or eliminating alcohol intake during treatment is recommended.

Treatment Issues for Recovering Addicts

For those in recovery from alcohol or drug use, relapse is a significant concern. Interferon's side effects have been compared to those of opioid withdrawal, which may trigger drug cravings. Interferon is given by injection, which may also be an issue for some recovering injection drug users.

HCV Treatment in Correctional Institutions

> *Correctional facilities are critical settings for the efficient delivery of prevention and treatment interventions for infectious diseases. Such interventions stand to benefit not only inmates, their families, and partners, but also the public health of the communities to which inmates return.*
>
> —T. M. Hammett
> *American Journal of Public Health*

Estimates of hepatitis C prevalence among the almost 2 million inmates of state and federal correctional facilities range from 255,000 to 500,000 (Allen 2003; CDC 2003). A serosurvey of 3,914 Maryland inmates reported that 29.7% had antibodies to hepatitis C (Goldstein 2003). Screening for and treatment of hepatitis C in correctional facilities is extremely inconsistent. According to results from a national survey from Spaulding and colleagues, only one state (Colorado) routinely screens for hepatitis C. California was the only state to perform a seroprevalence survey. A standard protocol for HCV treatment was followed by four states, while 73% of respondents "sometimes consider" treatment with interferon (Spaulding 1999). Data on treatment outcomes are available from Rhode Island; their Department of Corrections treated 90 inmates with interferon plus ribavirin; of the 41 who completed treatment, 26 (62%) achieved sustained virological response (Allen 2003).

Inmates have had to resort to litigation to obtain treatment for hepatitis C in Montana, Oregon and Pennsylvania (Gustavson 2003; J. Lin 2002; McKee 2002). Withholding necessary treatment from prisoners is unacceptable. A valuable tool for advocates comes from the Centers for Disease Control (CDC) in the form of guidelines for *Prevention and Control of Infections with Hepatitis Viruses in Correctional Settings*.

Alternative and Complementary Therapies

As practitioners educating and treating patients with liver disease, we are obliged to be informed about popular alternative therapies, understanding of our patients' need to be partners in their care, and open-minded to the possibility that some benefit may come from therapies currently regarded as alternative.

—N. M. Bass
Current Gastroenterology Report

Complementary and alternative treatments for liver disease come from many cultures. They may be useful as alternatives to standard HCV treatment, as adjunctive therapies, or to minimize the side effects of interferon and ribavirin.

At present, these therapies have not been adequately researched. The lack of standardization of these preparations, and the inconsistent manufacturing practices involved with their production, make it difficult to perform pharmacokinetic evaluations, safety and efficacy studies, and investigations of potential interactions.

In 1999, 809 individuals receiving care at six different liver clinics completed a questionnaire on their use of complementary and alternative medicine (CAM). Overall, 74% of respondents indicated CAM use, although 26% did not inform their physician. Silymarin (milk thistle) was used by 12% as a treatment for liver disease (Seeff 2001; Strader 2002). Silymarin has been used to treat liver disorders for at least 2,000 years, and has been reported to work as an antioxidant and have anti-inflammatory and regenerative properties. Silymarin may increase hepatocyte protein synthesis, decrease activity of tumor promoters, and protect against liver injury by blocking various toxins from entering liver cells (Flora 1998; Giese 2001; Luper 1998; Wellington 2001).

Conflicting results have emerged from two trials evaluating silymarin's effect on cirrhosis. Ferenci and colleagues randomized 170 individuals with varying degrees of cirrhosis (alcohol- and non-alcohol-related) to receive either 140 mg of silymarin three times daily, or a placebo for two years. After a mean observation period of 41 months, the survival rate in the silymarin group was 58 ± 9% vs. 39 ± 9% for the placebo group (P=0.036). A subgroup analysis revealed that silymarin appeared to be most beneficial for individuals who had alcoholic cirrhosis (P=0.03). No side effects were reported (Ferenci 1989). Pares and colleagues evaluated the effects of silymarin in 200 individuals with alcoholic cirrhosis, who were randomized to receive either 450 mg of silymarin thrice daily or placebo for two years. Survival was similar in treated and placebo groups, and no significant effect on the clinical course of liver disease was observed (Pares 1998). Two other studies have noted significantly reduced levels of ALT and AST in individuals with liver disease (Buzzelli 1993; Salmi 1982). So far, one study from the National Center for Complementary and Alternative Medicine (NCAM) examined the effect of silymarin in chronic hepatitis C. The estimated completion date for this study was June 2002. Results are not yet available.

Recommendations

Increase knowledge of treatment and care for hepatitis C patients among primary care providers.

Surveys of primary care providers have revealed significant gaps in the care and treatment provided to patients with hepatitis C. A national survey of primary care providers found that a quarter of the 1,412 physicians who responded did not know what treatment to recommend for hepatitis C (Shehab 2001). Provider education initiatives, such as continuing medical education credits (CMEs) are urgently needed.

Identify optimal dosing strategies for pegylated interferon and ribavirin.

Although there are approved doses for both brands of pegylated interferon (Pegasys® [pegylated interferon alfa-2a] and Peg-Intron® [pegylated interferon alfa-2b]), there are unresolved dosing issues with each product. The FDA has required that Roche and Schering conduct studies examining 1) the potential safety and efficacy of higher doses of Pegasys and/or ribavirin in people with genotype 1, high viral load, and weight >85 kg (Roche); 2) the safety and efficacy of fixed-dose (800 mg) vs. weight-based (800–1,400 mg) ribavirin in combination with Peg-Intron (Schering's WIN-R); and 3) the safety and efficacy of low-dose (1.0 ug/kg) vs. high-dose (1.5 ug/kg) Peg-Intron in combination with ribavirin for people with genotype 1 (Schering's IDEAL).

Dose reductions have occurred frequently during pivotal HCV treatment trials, yet data on efficacy and tolerability of lower doses of pegylated interferon alfa-2a are scarce. A 135 μg dose of pegylated interferon alfa-2a may be equally efficacious as, and more tolerable than a 180 μg dose (Pockros 2001).

As for pegylated interferon alfa-2b, pharmacokinetics data suggests that the once-weekly 1.0 μg/kg dose recommended for monotherapy may be suboptimal. The upper limit for weight-based dosing of pegylated interferon alfa-2b has not been adequately defined. Obese individuals typically have lower response rates, but it is unclear whether this is due to inadequate dosing of pegylated interferon and/or ribavirin or to other poor prognostic factors, viral resistance, or a combination of these elements.

Schering and Roche must support research to answer these questions.

Increase research on treatment safety and efficacy in understudied populations.

Most studies of HCV treatment efficacy and safety have focused on populations with favorable prognostic factors. Individuals with medical and psychiatric co-morbidities have been excluded from the pivotal studies of pegylated interferon and ribavirin, and results from these trials may not be applicable to a majority of individuals with HCV infection. More research is urgently needed on the safety, efficacy, and optimal dosing and duration of HCV treatment in African Americans, cirrhotics, active drug users, individuals on methadone maintenance, the mentally ill, transplant recipients, individuals with renal disease, individuals with autoimmune disorders, the elderly, young children, adolescents, and non-responders and relapsers after prior HCV treatment. This

research should be funded by NIH.

African Americans have been underrepresented in clinical trials. This may be attributed in part to the exclusion criteria for neutropenia, as African Americans are constitutionally neutropenic (Freedman 1997; Reed 1991; Zezulka 1987). Investigation of a safe threshold for neutropenia for African Americans, and modification of the standard exclusion criteria for neutropenia will help to minimize underrepresentation of African Americans in clinical trials.

Treatment should not be withheld from active drug users; decisions should be made on an individualized basis.

Treatment has traditionally been withheld from active drug users. A survey of 306 former IDUs in a methadone maintenance program revealed that 53% were interested in treating their HCV after hearing about the risks and benefits of interferon therapy (Stein 2001). Three studies have assessed feasibility, safety, and efficacy of HCV treatment in groups of individuals who were undergoing detoxification and/or receiving methadone maintenance, and a subset who were using drugs and/or alcohol during HCV treatment (Backmund 2001; Sylvestre 2002; Van Thiel 2003). Response rates from one trial were within the expected range from clinical trials of non-drug-using individuals (Backmund 2001; McHutchison 1998; Poynard 1998). Another study demonstrated that response rates to treatment were increased in individuals who had been drug-free for six months prior to treatment, yet a proportion of those who used drugs infrequently during HCV treatment still achieved SVR (Sylvestre 2002b).

The risk of reinfection is often used as a reason not to offer treatment to active injection drug users. So far, there has been scant documentation of reinfection in IDUs who achieved SVR after HCV treatment, although this may reflect the paucity of studies rather than the infrequency of reinfection. At any rate, provider concern should be focused on ensuring that injectors have access to sterile syringes by referral to syringe exchange programs (when possible) or pharmacy sale; other strategies include referral to methadone maintenance programs, prescription of buprenorphine and drug treatment upon request.

Develop integrated, multidisciplinary systems of care for individuals with multiple co-morbidities (HCV, mental illness, addiction).

Individuals with hepatitis C are often grappling with additional issues: the stress involved with illicit drug use; maintaining recovery from addiction; severe, debilitating fatigue; poverty; homelessness; or incarceration. HCV is more prevalent among the mentally ill, and individuals with HCV have a greater prevalence of depression (Zdilar 2000).

Our health care system is not prepared to accommodate the needs of active users or dually and triply diagnosed individuals. Multidisciplinary systems of care have been proven successful in treating active users, individuals with addiction and psychiatric co-morbidities, and individuals in a methadone maintenance program (Backmund 2001; Samet 2001; Samet 2003; Schwartzapfel 2002; Sylvestre 2002; Van Thiel 2003). Cross-disciplinary care must become an integral part of the care and treatment of people living with HCV.

Provide full access to hepatitis C care and treatment for all those in need.

Current treatments for HCV can cost up to $40,000 per year. The uninsured, underinsured, and those ineligible for patient assistance and entitlement programs go untreated, even when treatment is urgently needed. Advocacy efforts to increase access to HCV treatment must continue. Entitlement programs and private insurers should cover the costs of HCV treatment, including laboratory monitoring and medications to manage treatment side effects. Medicaid programs must receive the necessary funding from Congress to cover HCV treatment. Strategies must be developed to provide coverage for HCV therapy among the uninsured who do not qualify for entitlements or patient assistance programs.

Provide full access to hepatitis C care and treatment for incarcerated individuals.

In the United States, close to 2 million individuals are incarcerated. HCV infection is endemic among prisoners. A 1994 study of HCV prevalence among 4,513 inmates (87% male; 13% female) in the California correctional system reported that 39.4% of the males and 53.5% of the females were HCV-antibody-positive (Ruiz 1999). The need for HCV treatment remains largely unmet in correctional systems. Policies about HCV treatment in prison differ in every state, and incarcerated individuals do not have uniform access to treatment for HCV. Some inmates have had to resort to legal action to obtain treatment. This is an unacceptable situation. State and national advocacy efforts must be coordinated to demand access to HCV treatment for inmates. A valuable tool for advocates comes from the Centers for Disease Control (CDC) in *Prevention and Control of Infections with Hepatitis Viruses in Correctional Settings* (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5201a1.htm, accessed on 10 April 2004).

Increase research on strategies to manage side effects from HCV treatment.

The side effects of treatment for hepatitis C range from the uncomfortable to life-threatening. In a recent 1,100-person phase III trial of pegylated interferon alfa-2a (with placebo or ribavirin) and interferon alfa-2b, the rate of treatment discontinuation due to adverse events and/or laboratory abnormalities was 10% in the pegylated interferon/ribavirin arm and 11% in the standard interferon arm. Dose reductions were necessary for 32% of the individuals in the pegylated interferon/ribavirin arm (Fried 2002a). Significant dose reductions may have an impact on the response to treatment (Fried 2002a; McHutchison 2002).

A comparison of adverse events from a recent trial comparing peg-interferon alfa-2b and ribavirin to interferon alfa-2b and ribavirin found that more than 20% of participants in each arm experienced fatigue, headache, fever, muscle aches and stiffness, insomnia, nausea, hair loss, irritability, joint pain, loss of appetite and weight loss, depression, and injection site reactions (Manns 2001). The list of serious adverse events associated with interferon treatment, although occurring in less than 1% of individuals studied so far, is daunting and includes severe neuropsychiatric complications and suicidal ideation, as well as skin, kidney, blood, liver, heart, and autoimmune diseases, and sensory organ disorders (Fried 2002b).

Research on the safety and efficacy of interventions to increase the tolerability of, and adherence to, HCV treatment is a priority. More research is needed to identify the proper threshold to initiate

the use of growth factors to treat anemia and neutropenia, and to study their impact on HCV treatment efficacy. Interventions to decrease neuropyschiatric side effects are a priority: the instruments used to screen for depression have not been validated for this purpose. More exploration of the instruments used to diagnose depression and evaluate the efficacy, side effects, and indications of SSRIs, other antidepressants, and anti-anxiety agents is needed to optimize individual side effect management strategies.

The manufacturers of interferon, ribavirin, and ancillary mediations used as treatment for HCV treatment-induced side effects should provide the drugs, and their sponsorship to government-funded research networks so that additional strategies for side effects management may be developed.

Establish prospective, long-term follow-up studies to assess the durability and clinical benefit of histological responses in responders, relapsers, and non-responders.

Achieving a sustained virological response after HCV treatment increases the probability of histological improvement, but decreases in both grade and stage of liver disease have occurred in the absence of an SVR (Cammà 2004; Poynard 2002b; Shindo 2001). The risk of liver-related mortality from HCV appears to be lower among individuals who have been treated with interferon (Imazeki 2003). Longer follow-up of participants in pivotal HCV treatment trials will provide more information on the potential histological benefits of therapy, regardless of the response to treatment. Improvements in the grade of histological activity appear to occur most frequently among individuals treated with interferon plus high-dose ribavirin (Poynard 2002b). At present, there are not enough data to determine whether this post-treatment stabilization of HCV-related liver disease—especially in relapsers and non-responders—will confer clinical benefit. NIH should fund long-term research on the effect of HCV treatment on liver histology.

Evaluate durability and clinical benefits of sustained virological response.

Although many regard a sustained virological response as a "cure" or sign of remission, more data on the long-term outcomes of sustained virological responders are needed, especially in light of improved treatment efficacy and increased sensitivity of HCV-RNA assays.

Late relapse rates of up to 12% have been reported among sustained virological responders (Collier 2000; Pradat 2003). Low levels of HCV RNA have been detected in blood from 11 sustained virological responders up to five years after HCV treatment (Pham 2004). Industry-sponsored trials are ideal venues for establishing systems to collect data on long-term virological, histological, and clinical outcomes. NIH should support this research.

Identify when treatment for acute hepatitis C should be initiated, and what the optimal regimen and duration of therapy should be.

Treatment of acute HCV infection presents an opportunity for viral eradication; the rate of SVR in two recent studies ranged from 90% to 98% (Jaeckel 2001; Vogel 1996). These promising results require further study. Randomized, controlled trials of treatment of those with acute HCV are needed to define the interval during which spontaneous viral clearance is likely to occur, so that treatment may be initiated in the absence of spontaneous viral clearance. Optimal regimens and

duration of treatment should be identified. Roche and Schering should support this research.

Create an "opt-out" system for organ donation in the United States and include discussion of organ donation as part of school health education programs and regular medical care.

Between 1988 and 1999, the number of liver transplants in the United States increased from 1,713 to 4,689, and the number of centers performing liver transplantation rose from 59 to 117 (C. M. Smith 2000). As of June 30th, 2003, 17,001 Americans were awaiting liver transplantation. In the period between July 1, 2003 and June 30, 2003, only 5,486 had a liver transplant; 1,772 others died while waiting for a liver (Scientific Registry of Transplant Recipients, 2004). Many of these individuals would still be alive today if the supply of donor organs was adequate, as the one-year survival rate for HCV-related liver transplantation is 86.4% (Scientific Registry of Transplant Recipients, 2002; C. M. Smith 2000; United Network for Organ Sharing, 2000). It is estimated that, if untreated, the proportion of persons with HCV who will develop cirrhosis by 2020 will increase from 16% to 32%. Complications of cirrhosis, such as hepatic decompensation, hepatocellular carcinoma, and liver-related deaths will increase by 106%, 81%, and 180%, respectively (Davis 2003a). Increasing the supply and accessibility of available donor organs is an urgent priority. In the United States, potential organ donors may opt-in. Switching to a system that assumes organs will be donated unless an individual specifically opts-out will save lives.

A discussion of organ donation should be incorporated into school health education initiatives and primary care visits, so that it becomes normalized and premeditated, instead of being associated with shock, grief, and loss.

Research safety and efficacy of alternative therapies for HCV infection.

A national survey assessing the use of complementary and alternative therapies found that 42% of Americans reported use of complementary and alternative medicine (CAM); and an estimated 41% of individuals receiving care at six liver disease clinics reported use of CAM (Seeff 2001). Despite this widespread usage, we do not have data on the safety and efficacy of these therapies. The National Center for Complementary and Alternative Medicine (NCCAM) has performed a few exploratory studies of silymarin and mixed herbs for treatment of hepatitis C; we need larger, more rigorous investigation of pharmacokinetics, potential interactions, and safety and efficacy of complementary and alternative therapies in the treatment of hepatitis C. NIH should support this research.

List of Terms Used in This Chapter

Apoptosis: programmed cell death.

Estradiol: a female steroid sex hormone, is the most potent form of estrogen. It has many important functions, including growth of the uterus, fallopian tubes and vagina.

Half-life: the time needed for half of something to be eliminated from the bloodstream.

Hepatocytes: liver cells.

Intent-to-treat: an analysis of clinical trial results that includes all data from trial participants in the groups that they were randomized to, even if they never received the treatment or completed the trial.

MIU: million International Units. An International Unit is a measurement of the amount of the biologically active substance in the standard amount of the preparation producing this activity—such as a vitamin—that is agreed upon as an international standard, especially for comparison with other biologicals containing the substance. Internal Units are also used in Hepatitis C viral load testing; the results are usually reported as International Units per milliliter (IU/mL).

MU: million units.

Progesterone: Progesterone is a female steroid sex hormone that prepares the uterus for pregnancy, primes the breasts for making milk and protects the developing fetus.

Virion: an individual virus particle.