VII. Hepatitis C Treatment in HIV/HCV Coinfection

The burden of liver disease is too high to delay management of HIV/HCV coinfected persons while awaiting better data. Instead, the management of hepatitis C today must be based on data generated on persons without HIV and an understanding of both infections.

—David L. Thomas
Hepatology

Summary

Hepatitis C progresses more rapidly in coinfected persons (see Chapter III, Natural History of HIV/HCV Coinfection); consequently, the need for information about the safety and efficacy of HCV treatment in coinfection is urgent. Three key studies of HCV treatment in coinfected persons—the Adult AIDS Clinical Trials Group's A5071, Roche's Apricot and the ANRS HC02 (RIBAVIC)—have reported that pegylated interferon-based regimens are more effective than standard interferon-based regimens, although sustained virological response rates have been lower in these coinfection treatment trials than in HCV monoinfection treatment trials (Chung 2002b; Chung 2004; Perronne 2002; Perronne 2004; Torriani 2004).

Tolerability of and access to treatment for HCV are pressing issues for coinfected people, who tend to experience more severe side effects from HCV treatment. Significant interactions between ribavirin and didanosine (ddI; Videx®) have been reported, and ribavirin may exacerbate toxicities of other antiretrovirals. Discontinuations from clinical trials of pegylated interferon-based regimens have been a significant problem; dropout rates have been as high as 30–46% (Hopkins 2002; Perronne 2002; Rockstroh 2002). Access to HCV treatment is limited: currently, only 14 state AIDS Drug Assistance Programs (ADAPs) in the U.S. have been able to add pegylated interferon and ribavirin to their formularies. Twenty-three states have no plans to cover these drugs in the future, due to financial constraints (National ADAP Monitoring Project 2004). Insufficient federal and state funding of ADAPs may further limit access to HCV treatment. Expected cuts in Medicaid funding may also limit access to HCV treatment for many coinfected individuals in the U. S.

Up to 90% of people who acquired HIV from injection drug use are coinfected with hepatitis C (CDC 2002f). Although injection drug use is no longer a contraindication for HCV treatment, injection drug users still encounter significant barriers to obtaining treatment for HCV and HIV. HIV-positive and HIV/HCV coinfected injection drug users have generally received HAART later than non-users. (Bassetti 1999; Bogart 2000; Hare 2002; Maisels 2001; Mocroft 1999a; Murri 1999 Sulkowski 2002; Tedali 2003a; Tedali 2003b; Torriani 2001; Qurishi 2002a; Qurishi 2002b). These barriers may be attributable in part to discomfort reported by physicians who provide care to people with drug and/or alcohol problems, as well as inadequate training on assessment of and interventions for addiction (M. F. Fleming 1999; N. S. Miller 2001; Saitz 2002). Harm reduction strategies— referral to drug/alcohol treatment upon request, instruction on safe injection practices, referral to syringe exchange programs, methadone maintenance and prescription of buprenorphine—must be incorporated into the medical care of coinfected injection drug users.

The safety and efficacy of treatment for hepatitis C have not been adequately assessed in populations with high prevalence of HIV/HCV coinfection, such as hemophiliacs, individuals with psychiatric disorders and active drug users. There is limited information on treatment outcomes in coinfected cirrhotics. Successful outcomes have been reported from uncontrolled studies of treatment for acute HCV infection in HIV-positive persons, but the optimal regimen and duration of therapy are unknown.

Promising data has emerged from studies of coinfected liver transplant recipients, although access to transplantation is limited for HIV-positive candidates, and treatment for recurrent hepatitis C remains problematic.

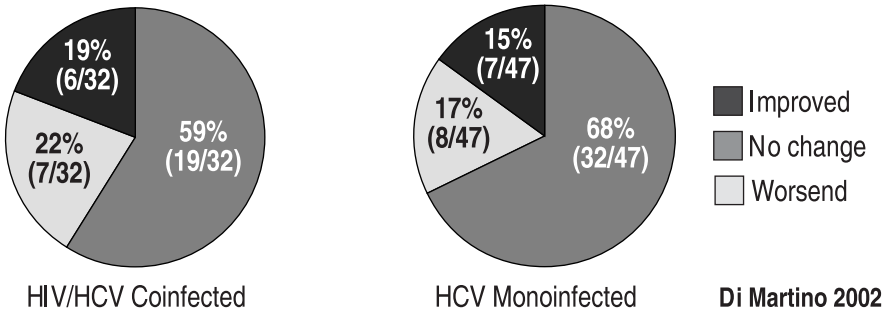
Interferon Monotherapy

Early studies of interferon monotherapy for treatment of HCV in HIV-positive individuals yielded sustained virological response (SVR) rates ranging from 22.5% to 30% (Mauss 1998; Soriano 1996).

- Histological Benefit of Interferon Monotherapy In Coinfection

A study from Di Martino and colleagues selected decrease in fibrosis score and reduction in disease activity after HCV treatment as the primary endpoints. A group of 79 injection drug users, 32 coinfected, received 3 MIU of interferon alfa-2b thrice weekly for 24 weeks. There was no significant difference in histological response or fibrosis score according to HIV status, nor was any relationship between CD4 cell count and histological response identified. Liver biopsies were performed at baseline and again at 23 ± 16 months after completion of treatment. Histological response was defined as a decrease in the Knodell score (see Chapter IV, Diagnostics) of >2 points; fibrosis improvement was a decrease in fibrosis score of >1. There were no significant differences in histological response by HIV status (40.6% [13/32] vs. 36.2% [17/47] for HCV alone). Predictors of histological response to treatment were: presence of a biochemical response to treatment (OR, 4.9; P=0.008), baseline HCV RNA <1,000,000 (OR, 4.1; P=0.023) and a high pretreatment Knodell score (P=0.0002).

Figure 1. Changes in Fibrosis Score After HCV Treatment



Predictors of improvement of fibrosis were biochemical response to treatment (OR, 4.6; P=0.039), non-1 HCV genotype (OR, 8.6; P=0.023), and a high pretreatment liver fibrosis score (P<0.0001) (Di Martino 2002). Long-term follow-up is needed to assess the durability of improvements in liver histology among coinfected persons.

Combination Therapy

Data from HCV monoinfection treatment trials indicated that adding ribavirin to interferon improved treatment efficacy (see Chapter V, HCV Treatment). Subsequent studies in coinfected individuals have investigated the safety and efficacy of combination therapy. While interferon-based regimens are no longer the standard of care for HCV treatment, these studies have yielded useful data about tolerability, drug interactions, adverse events and the relationship of CD4 cell count to treatment efficacy.

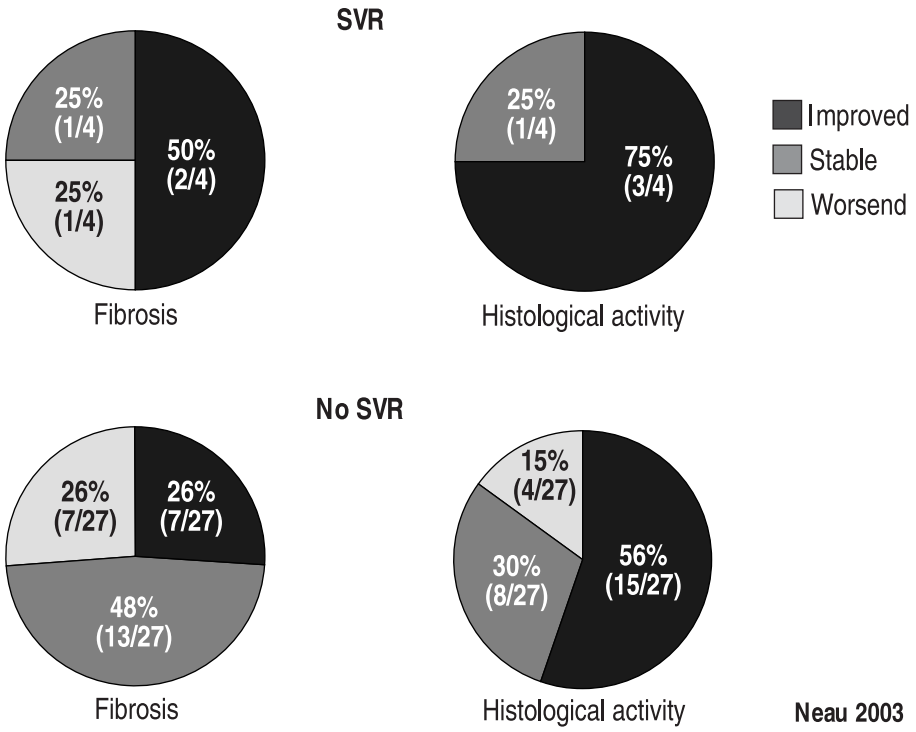
Table 1. Sustained Virological Response (SVR) Rates: Combination Therapy with Standard IFN + RBV

Author	Regimen & Duration	N Participants	CD4 Count	SVR	Discontinuation
Bochet 2001	IFN 3 MIU 3xweek + RBV 800–1200 mg/day For 6 months (10), 9 months (3), and 12 months (25)	Total N=56 treatment naïve: 54% (30/56) non-responders: 46% (20/56)	377 ± 27	Overall: 17.8% No difference by treatment experience	27% (15/56) For: anemia, depression, asthenia, anger, neuropathy
Nasti 2001	IFN alfa-2b 3 MIU 3xweek + RBV 1000–1200 mg/day For 24 weeks	N=17	Mean:445 SD: 144	19% (3/17)	6% (1/17) For: mild dizziness (interfered with ability to work)
Landau 2001	IFN alfa-2b 3 MIU 3xweek + RBV 1000–1200 mg/day For 12 months	N=51	412 ± 232	21% (11/51)	29% (15/51) For: adverse events (4) virological non-response (11)
Pérez-Olmeda 2002 Arm A	IFN 3 MIU 3xweek + RBV 800 mg/day For 6 months	Total N=111	>350	22% (24/111)	12% (13/111) For: adverse events (not specified)
Arm B	INF 6 MIU/day for 6 weeks, then cross over to Arm A regimen				
Santos 2002	IFN 3 MIU 3xweek + RBV 1000–1200 mg/day Genotypes 1&4: for 12 months Genotypes 2&3: for 6 months	Total N=26 Genotype 1: 13 Genotype 4: 2 Genotype 2: 1 Genotype 3: 10	Mean:632	27% (7/26) Genotypes 1&4: N=2 Genotype 3: N=5	15% (4/26) For: 'flu-like' syndrome (3) suicide (1)
Sanchez Montero 2002	IFN 3 MIU 3xweek + RBV 800 mg/day For 24 weeks	N=21	>350	43% (9/21)	None reported
Sulkowski 2003b Arm A	IFN 3 MIU 3xweek + RBV 800 mg/day For 48 weeks	Total N=180	Mean:533	4.3%	Virological non-response: 43% (39/90)
Arm B	IFN 3 MIU daily + RBV 800 mg/day For 48 weeks		Mean:551	9.3%	Virological non-response: 20% (18/90)
Braü 2004 Arm A	IFN 3 MIU 3xweek + RBV 800 mg/day For 48 weeks	N=53	Mean:458	11% (6/53)	Discontinued: 51% (55/107) for adverse events: depression, anxiety, anemia and fatigue: 21% (23/107) insufficient response: 11% (12/107) lost to follow-up: 12% (13/107) relapse to active drug use: 4% (4/107)
Arm B	IFN 3 MIU 3xweek for 16 weeks; then added RBV 800 mg/day for another 32 weeks	N=54	Mean: 520	6% (3/54)	

Histological Outcome of Combination Therapy in Coinfection

Although the virological response rate was disappointing—only 15% (11/68) achieved SVR—valuable histological data emerged from a small study comparing two different regimens of standard interferon (ribavirin was added at week 12 if HCV RNA was detectable). Paired biopsy specimens were available from 31 participants, four of whom achieved an SVR (Neau 2003).

Figure 2. Histological Responses at Week 72



Host determinants for achieving histological response—improvement in fibrosis and/or decreased necroinflammatory activity—have yet to be identified. Predicting the likelihood of histological response, especially in the absence of a virological response, will help guide decisions about continuation of HCV treatment.

Efficacy and Safety of Pegylated Interferon and Ribavirin in Coinfection

Early Viral Kinetics

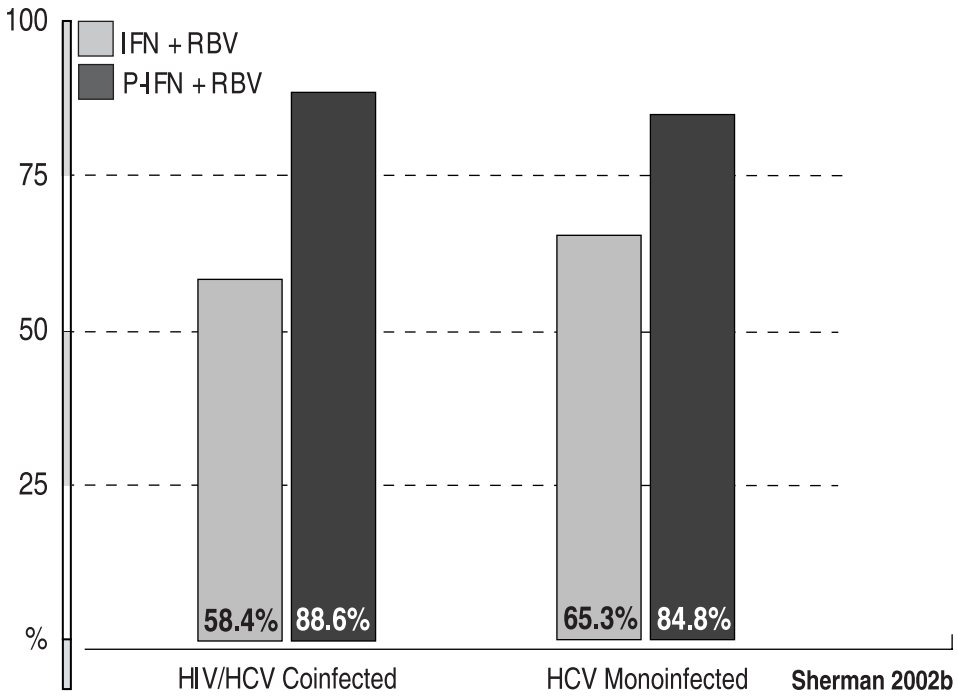
Viral clearance as early as 24 hours after initiating interferon-based treatment for hepatitis C may help to predict SVR in HCV monoinfection. Evaluating early responses to treatment in persons with HIV/HCV co-infection may offer information about the likelihood of HCV treatment efficacy, an opportunity for interventions to increase treatment efficacy, and spare those who are unlikely to benefit from treatment.

The decay rate of hepatitis C virions during early HCV treatment appears to be less rapid in coinfected individuals. In a viral kinetics substudy, three of ten coinfected persons (two of whom

received pegylated interferon) had a slow clearance of HCV. The interval before any reduction in HCV RNA was observed ranged from six days to more than twelve weeks (Torriani 2003). A look at hepatitis C viral decay during early HCV treatment in five coinfected individuals found a virion half-life of 7.0 ± 1.0 hours (vs. a virion half-life of two to three hours in HCV monoinfection) (Layden 2002b; Torriani 2002a).

Reports from two small studies of viral kinetics during the first 72 hours of HCV treatment reflect the superior efficacy of pegylated interferon despite the longer viral half-life of HCV observed in coinfected persons. Sherman and colleagues studied ten coinfected individuals; five received standard interferon alfa-2a and ribavirin, five pegylated interferon alfa-2a with ribavirin. Although the initial viral response was slightly delayed among individuals treated with pegylated interferon alfa-2a (9 hours vs. 7.7 hours for standard interferon), pegylated interferon increased the efficiency of initial-phase viral clearance from 65% (standard IFN) to 90% ($P<0.05$) (Sherman 2002b). In another study, Sherman and colleagues evaluated early viral clearance among 27 individuals (12 coinfected) treated with standard or pegylated interferon-based regimens. HCV RNA testing was performed at 0, 6, 12, 24, 48 and 72 hours. Again, pegylated interferon was more efficient than standard interferon, regardless of HIV status ($P<0.05$) (Sherman 2003).

Figure 3. Efficiency of Viral Clearance at 72 Hours by Regimen and HIV Status



Ballestros and colleagues studied early viral kinetics of hepatitis C in 28 coinfected persons treated with pegylated interferon alfa-2b (1.5 mg/kg once weekly) and ribavirin (800 mg/day). During the first 24 hours of treatment, viral kinetics differed significantly between responders and non-responders, and according to HCV genotype. Within the first 24 hours of treatment, the decrease in HCV RNA was significantly greater among virological responders than non-responders (-1.06 $\log_{10}$ vs. - 0.05 log 10; $P=0.002$). Sustained virological responders maintained lower levels of HCV RNA throughout treatment (24 weeks for genotype 3 and 48 weeks for genotypes 1 and 4). The

median decrease in HCV RNA during the first 24 hours of treatment differed significantly by HCV genotype (-1.20 log_{10} in genotype 3 vs. –0.06 log_{10} in genotype 1 and –0.37 log_{10} in genotype 4; P=0.022). SVR could be predicted by virological response at week 4; 100% of people who achieved either a two-log decrease or undetectable HCV achieved SVR, while 92.9% (13/14) of week 4 non-responders did not achieve SVR (Ballestros 2004). A greater number of sustained virological responders in this study had genotype 3 (60% [6/10] vs. 11.1% for both genotypes 1 and 4 [1/13 and 1/5, respectively]). The predictive value of week 4 virological response may be more applicable in genotype 3 than genotypes 1 and 4.

Coinfection Treatment Trials

The efficacy of pegylated interferon plus ribavirin in HCV monoinfection warranted investigation in coinfected individuals. Although a wealth of natural history data have established that HCV is more aggressive in people with HIV, studies of safety and efficacy of pegylated interferon-based regimens in coinfected persons have lagged years behind pivotal monoinfection treatment trials. Long-overdue data on the safety and efficacy of pegylated interferon plus ribavirin in coinfected persons from three randomized, controlled coinfection treatment trials (Roche's APRICOT, the ACTG's A5071 and ANRS HC02/RIBAVIC) were presented in February of 2004. All reported that pegylated interferon-based regimens are more effective for coinfected persons than standard interferon-based regimens, although less effective for coinfected persons than those with HCV alone (Chung 2004; Perronne 2004; Torriani 2004).

Table 2. Sustained Virological Response Rates From HCV Treatment Trials of Pegylated Interferon-Based Regimens by HIV Status and HCV Genotype

Author	Population	Regimen	Duration	N Participants	% SVR		
					Overall	Genotype 1	Genotypes 2&3
Fried 2003	HCV	P-IFN alfa-2a 180 µg 1xweek + 1,000–1200 mg RBV/day	48 weeks	N=453	56%	44%	70% (includes genotypes 4, 5 & 6)
Hadziyannis 2004	HCV	P-IFN alfa-2a 180 µg 1xweek + 1,000–1200 mg RBV/day	48 weeks	N=424	61%	51%	80%
Manns 2001	HCV	P-IFN alfa-2b 1.5 mg/kg 1xweek + 800 mg RBV/day	48 weeks	N=511	54%	42%	82%
Chung 2004	HIV/HCV	P-IFN alfa-2a 180 µg 1xweek + 600 up to 1,000 mg RBV/day*	48 weeks	N=66	27%	14%	73%
Perrone 2004	HIV/HCV	P-IFN alfa-2b 1.5 mg/kg 1xweek + 800 mg RBV/day	48 weeks	N=205	27%	15%	44%
Torriani 2004	HIV/HCV	P-IFN alfa-2a 180 µg 1xweek + 800 mg RBV/day	48 weeks	N=289	40%	29%	62%

*In A5071, ribavirin dose was gradually escalated by 200 mg every four weeks, as tolerated.

As in HCV monoinfection, genotype appears to be the most significant prognostic factor for a sustained virological response to treatment (Chung 2002b; Chung 2004; Fried 2002; Hadziyannis 2004; Hopkins 2003; Manns 2001; Pérez-Olmeda 2003b; Perronne 2002; Perronne 2004; Torriani 2004; Voigt 2003).

Since the treatment regimen, sample size and baseline characteristics of participants differed, direct and accurate comparisons of these trial results are not possible. Although ACTG A5071 and APRICOT used pegylated interferon alfa-2a, the initial dose of ribavirin was lower in A5071 than APRICOT (600 mg/day, gradually escalated by 200/mg day every four weeks vs. 800 mg/day). ANRS HC02 used pegylated interferon alfa-2b. The ribavirin dose in ANRS HC02 and APRICOT was the same (800 mg/day), but ribavirin dose reductions may have occurred more frequently in ANRS HC02, because it did not allow the use of growth factors to treat anemia, whereas the other two studies did.

Although all participants in APRICOT, ACTG A5071 and APRICOT were coinfected, some of their other characteristics varied; ANRS HC02 had a greater proportion of cirrhotics than the other two studies, while ACTG A5071 had a greater proportion of black participants (HCV treatment is less effective for cirrhotics than those with less advanced liver disease, and less effective for Blacks than non-Blacks). Well-controlled HIV disease and mild-to-moderate liver disease of participants were reflected by response rates in APRICOT.

APRICOT

Roche sponsored APRICOT (AIDS Pegasys Ribavirin International Coinfection Trial), an 868-person, multi-site, randomized, controlled study, comparing safety and efficacy of 48 weeks of treatment with:

- Pegylated interferon alfa-2a (180 μg once weekly) plus placebo;
- Pegylated interferon alfa-2a (180 μg once weekly) plus ribavirin (800 mg per day); and
- Interferon alfa-2a (3 MIU, thrice-weekly) plus ribavirin (800 mg per day).

Table 3. Baseline Characteristics in APRICOT by Treatment Arm

	IFN + RBV (N=285)	P-IFN + placebo (N=286)	P-IFN + RBV (N=289)
Male	81%	82%	80%
White	78%	79%	80%
Using ART	84%	85%	84%
CD4 cell count (mean)	542	530	520
CD4 <200μL	7%	5%	6%
HIV RNA (mean ±SD)	2.3 ± 1.0	2.4 ± 1.0	2.3 ± 1.0
HIV RNA <50 copies/mL	60%	60%	60%
HCV RNA (mean)	5.2	6.3	5.6
Genotype 1	60%	61%	61%
Genotypes 2 and 3	31%	32%	32%

Torriani 2004

Coinfected individuals who had stable HIV disease (with or without antiretroviral therapy) and a CD4 cell count of either >200/mL or 100–200/mL with an HIV RNA of <5,000 copies/mL were eligible for APRICOT. Participants were required to be HCV treatment naïve. A liver biopsy within 15 months of study entry was required. Cirrhotics with Child-Pugh Grade A (see Chapter IV, Diagnostics) were eligible. APRICOT stratified by genotype (1 vs. non-1), baseline CD4 count (≥ 100–200/mL vs. ≥ 200/mL), antiretroviral therapy vs. no antiretroviral therapy, presence or absence of cirrhosis, and geographic region.

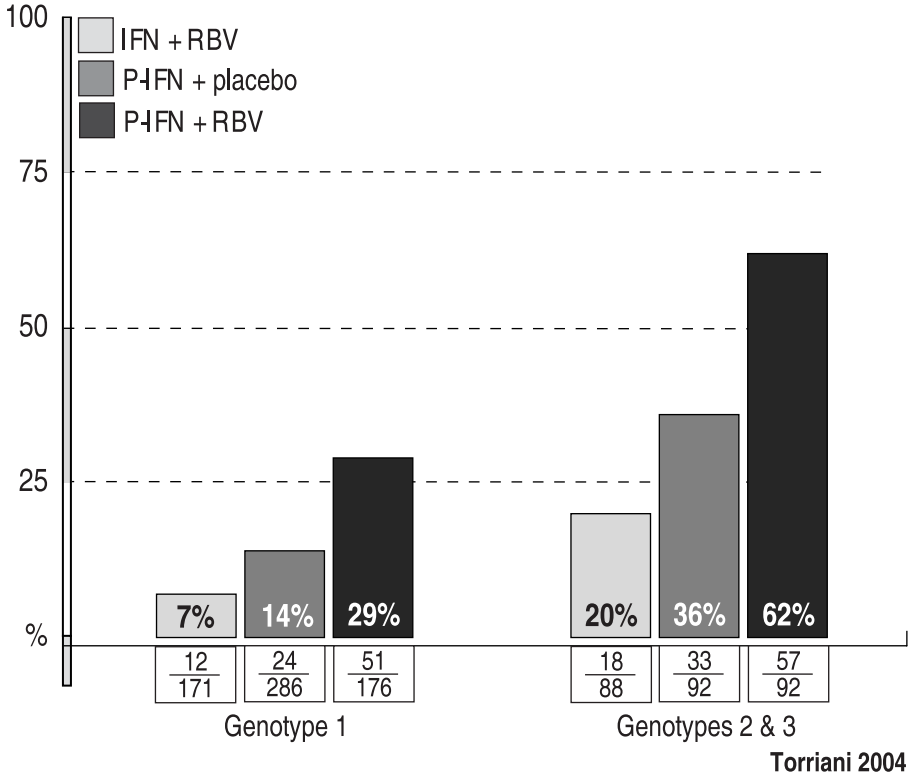
Although 24 weeks of therapy is the standard of care for HCV-monoinfected persons with genotype 2 or genotype 3, all of APRICOT's participants were treated for 48 weeks, regardless of their HCV genotype. The relapse rate (between the end of treatment and week 72) varied according to genotype and regimen. It was highest among participants with genotypes 2 and 3 who received pegylated interferon plus placebo, and lowest among those with genotypes 2 and 3 who received pegylated interferon plus ribavirin.

Table 4. APRICOT: End of Treatment (ETR) and Sustained Virological Response Rate (SVR) by Regimen and Genotype

	IFN + RBV		P-IFN + placebo		P-IFN + RBV	
	ETR	SVR	ETR	SVR	ETR	SVR
Genotype 1	8%	7%	21%	14%	38%	29%
Genotypes 2&3	27%	20%	57%	36%	64%	62%

Torriani 2004

Figure 4. APRICOT: Sustained Virological Response Rate (SVR) by Regimen and Genotype



Rodriguez-Torres and colleagues examined virological responses at week 12 and week 24 among 289 APRICOT participants randomized to pegylated interferon plus ribavirin. As in HCV mono-infection (Fried 2002), coinfected participants in APRICOT who did not achieve a ≥ 2 log decrease or undetectable HCV RNA by week 12 were extremely unlikely to achieve SVR (Rodriguez Torres 2004). Unfortunately, the positive predictive value of a virological response at week 12 or week 24 was less robust, especially among those with genotype 1 (Rodriguez Torres 2004).

Table 5. Predictive Value of Early Virological Response (EVR) at Week 12 and Week 24 (P-IFN + RBV only)

	EVR		SVR W 72	Negative Predictive Value		Positive Predictive Value	
	W 12	W 24		W 12	W 24	W 12	W 24
All	71% (204/289)	75% (216/289)	40% (116/289)	98%	99%	56%	53%
Genotype 1	63% (110/176)	68% (120/176)	29% (51/176)	98%	100%	45%	43%
Genotypes 2&3	84% (88/95)	85% (89/95)	62% (59/95)	100%	100%	70%	69%

Rodriguez Torres 2004

With regard to HIV, absolute CD4 cell counts decreased during treatment, but returned to baseline by week 72. The median decrease in CD4 cell counts at week 48 was greatest among those on pegylated interferon and ribavirin ([approximately] -140 vs. -120 for interferon plus ribavirin and pegylated interferon plus placebo). The CD4 percentage rose during treatment, peaked at week 36, and returned to baseline by week 72. HIV RNA decreased slightly during treatment in both of the pegylated interferon arms, and returned to baseline by week 72. It remained stable among those receiving interferon plus ribavirin.

The most common adverse events were fatigue and a constellation of flulike symptoms, insomnia, and depression. Serious adverse events possibly or probably related to HCV treatment were reported in 5% of the interferon arm, 10% of the pegylated interferon arm and 8% of those receiving pegylated interferon plus ribavirin. Two deaths (cardiac arrest and suicide during hospitalization for depression) occurred during APRICOT; both were considered possibly or probably related to study drugs (Torriani 2004).

Table 6. Treatment Discontinuation by Cause and Regimen

	IFN + RBV	P-IFN + placebo	P-IFN + RBV
Laboratory abnormality	0%	5%	3%
Adverse event	14%	12%	12%
Non-safety	24%	15%	10%

Torriani 2004

AACTG A5071

In the Adult AIDS Clinical Trials Group's A5071 study, 132 coinfected study volunteers were randomized to 24 weeks of treatment with:

- Pegylated interferon alfa-2a (180 μg once weekly) plus ribavirin (600 mg per day, increased by 200 mg every four weeks as tolerated, to a maximum of 1,000 mg/day); or
- Interferon alfa-2a (6 MIU, thrice-weekly for 12 weeks, then 3 MIU, thrice-weekly) plus ribavirin (600 mg per day, increased by 200 mg every four weeks as tolerated, to a maximum of 1,000 mg/day).

Table 7. Baseline Characteristics in 5071 by Treatment Arm

	IFN + RBV (N=67)	P-IFN + RBV (N=66)
Male	85%	79%
White	46%	50%
African American	34%	32%
Hispanic	12%	15%
Using ART	87%	85%
CD4 cell count (median)	444	482
HIV RNA >50 copies/mL	60%	61%
HCV RNA IU/mL	6.2 ± 0.3	6.2 ± 0.4
Genotype 1	78%	77%
Median fibrosis score	2.0 out of 6.0	2.0 out of 6.0
Cirrhosis	9%	11%

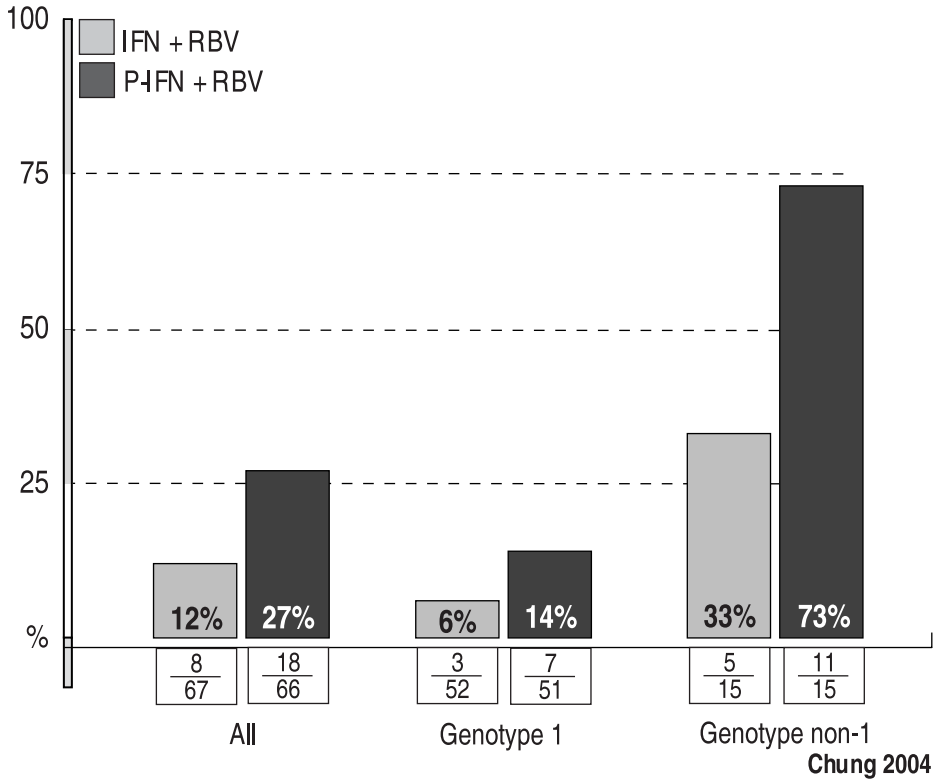
Chung 2004

Coinfected individuals who were on stable antiretroviral therapy for at least 12 weeks and had a CD4 cell count of >100 and an HCV RNA <10,000 were eligible for 5071. If the People with a CD4 cell count of >300 were eligible for A5071 if they had not received HIV treatment for 12 weeks before entering the study, and did not plan to start treatment for 24 weeks. Unless contraindicated, liver biopsy within a year of study entry was a prerequisite for participation. Compensated cirrhotics were eligible for 5071.

The primary endpoint of A5071 was the virological response at week 24. At week 24, participants with undetectable HCV RNA continued treatment for an additional 24 weeks, while people with detectable HCV RNA had a liver biopsy to assess histological response. Participants whose histological activity score decreased by at least two points from baseline continued treatment. Treatment was discontinued only for virological and histological non-responders.

Participants were stratified by HCV genotype (genotype 1 vs. non-1) and whether or not they were receiving antiretroviral therapy.

Figure 5. Sustained Virological Response by Genotype and Regimen: A5071

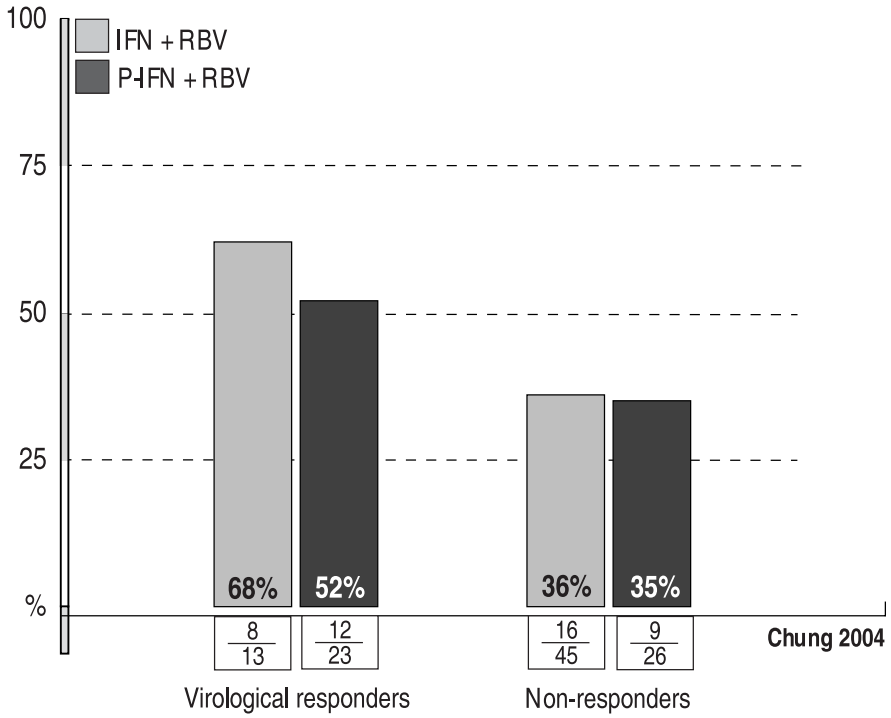


After controlling for other factors, independent predictors of a sustained virological response in A5071 were: a non-1 genotype (OR, 15.8; 95% CI, 4.94–50.5; P<0.001) treatment with pegylated interferon (OR, 4.76; 95% CI, 1.49–15.2; P=0.008), detectable HIV RNA at baseline (OR, 3.55; 95% CI, 1.19–10.6; P=0.023). Those with no history of injection drug use (IDU) were more likely to achieve SVR (OR, 0.48; 95% CI, 0.27–0.83; P=0.009) than current or former IDUs. Age, race, use of antiretroviral therapy with or without a protease inhibitor, CD4 cell count, baseline HIV RNA, liver histology and use of growth factors were not predictive of SVR (Chung 2004). This may be due to the small sample size and low SVR rate (26/133).

The relationship between previous injection drug use and treatment outcomes needs further exploration in larger studies. Depression may be a confounding factor, since it is a common side effect of interferon and is prevalent among IDUs with hepatitis C and HIV/HCV (Golub 2004, M. E. Johnson 1998; Garcia 2004). Interferon-induced or exacerbated depression may have had an effect on adherence to HCV treatment and/or study discontinuation. In A5071, treatment-related moderate-to-serious depression was reported among 18 study participants, some of whom may have had a history of IDU.

Although sustained virological response rates—particularly in genotype 1— were disappointing, a proportion of virological non-responders in each treatment arm derived histological benefit from treatment. Histological improvement was defined as a decrease in the HAI score of two or more points from the pre-treatment liver biopsy; see Chapter IV, Diagnostics. All histological responders had slight decreases in HCV RNA by week 24 (-0.61 with interferon; -1.01 with pegylated interferon), although these decreases did not differ significantly from those in histological non-responders (-0.58 with interferon; -0.71 with pegylated interferon).

Figure 6. Histological Improvement by Treatment Arm and Virological Response



During HCV treatment, absolute CD4 cell counts decreased, but they returned to slightly above baseline by week 72. The higher the CD4 cell count at study entry, the greater the decrease: people with CD4 cell counts above 700 at entry had decreases of 390 (pegylated interferon) vs. 149 (interferon), while individuals with CD4 cell counts under 700 at study entry had decreases of 111 (pegylated interferon) vs. 77 (interferon). As absolute CD4 cell counts dropped, the percentage of CD4 cells increased. After 24 weeks of treatment, the CD4 cell percentage rose by 2.5% in the standard interferon arm and 3.5% in the pegylated interferon arm. By week 72, CD4 cell percentages had returned to near-baseline levels. No opportunistic infections were reported during treatment or the follow-up period (Chung 2002b; Chung 2004).

Virological response at week 12 had a negative predictive value of 100%. In other words, the likelihood of achieving a sustained virological response without achieving either a two-log decrease or an undetectable HCV RNA by week 12 was zero percent. For week-12 virological responders, the likelihood of achieving SVR was 51%.

Moderate to severe flulike symptoms and depression were the most commonly reported side effects. Laboratory abnormalities occurred in both study arms. There were eight withdrawals (or 12%) from each study arm (Chung 2004).

Table 8. Laboratory Abnormalities in A5071 by Regimen and Severity*

	Grade 2: Moderate		Grade 3: Severe		Grade 4: Potentially life threatening	
	IFN	P-IFN	IFN	P-IFN	IFN	P-IFN
Anemia	1	0	0	0	0	3
Neutropenia	11	20	9	24	3	9
Thrombocytopenia	2	13	0	2	0	1
Glucose	18	17	3	7	0	5
ALT	13	23	7	4	1	0
Lipase	8	8	4	5	0	0
Lactate	0	0	1	0	0	0

Chung 2004

*from initiation of HCV treatment until week 72.

ANRS HC02 (RIBAVIC)

In ANRS HC02, 412 HIV/HCV-coinfected participants were randomized to 48 weeks of treatment with:

- Pegylated interferon alfa-2b 1.5μg/kg once weekly plus 800 mg/day of ribavirin; or
- Interferon alfa-2b 3MU three times per week plus 800 mg/day of ribavirin.

Table 9. Baseline Characteristics in ANRS HC02

Baseline Characteristics	
Male	74%
IDU (current or former not specified)	79%
Using ART	82%
CD4 cell count (mean)	541 ± 229/mL
HIV RNA <400 copies/mL	66%
Mean HIV RNA (if >400 copies/mL)	3.7 ± 0.7 log
With a previous AIDS-defining condition	17%
HCV RNA (mean)	5.9 ± 0.7 log
Genotype 1 or 4	58%
Genotype 3	34%
With bridging fibrosis or cirrhosis	39%

Perronne 2004

Coinfected persons with a CD4 cell count >200/mL and stable HIV disease (defined as no change in HIV RNA of ≥ 1 $\log_{10}$ within three months of study entry) were eligible, whether or not they were using antiretroviral therapy. Participants were required to be HCV treatment-naïve, and to have had a liver biopsy within 18 months of study entry.

The failure to achieve an SVR was most reliably predicted by the virological response (defined as either a two-log decrease in HCV RNA, or an undetectable HCV RNA) at week 12, while the virological response at week 4 was more likely to predict SVR. The negative predictive value of virological non-response at week 4 was 79%; it increased to 94% at week 12. The positive predictive value of an early virological response decreased from 92% at week 4 to 74% at week 12.

Figure 7. ANRS HC02: Sustained Virological Response Rate by Genotype and Regimen

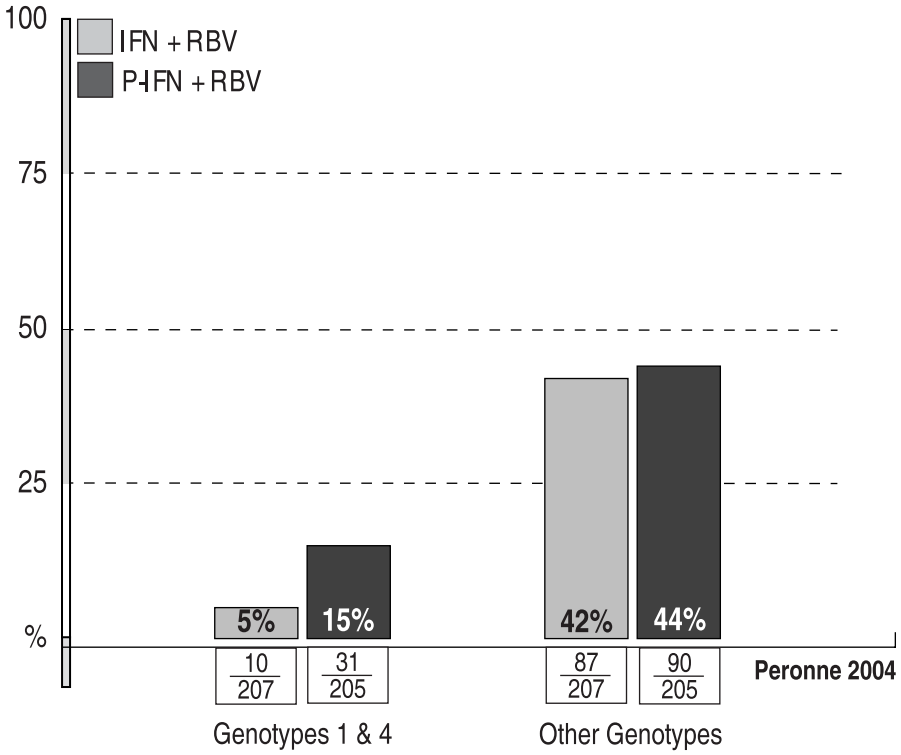


Table 10. ANRS HC02: Discontinuations and Sustained Virological Response Rate by Regimen, METAVIR Score, Baseline HCV RNA and Baseline CD4 Count

Variable	IFN + RBV (N=207)	P-IFN + RBV (N=205)
All	19% (39/207)	27% (55/205)
Completed treatment	28% (33/117)	36% (42/117)
% (N) who achieved SVR		
HCV RNA <1 X 10^6	23% (48/207)	28% (57/205)
HCV RNA >1 X 10^6	17% (35/207)	26% (53/205)
METAVIR score F0–F2	21% (44/207)	25% (51/205)
METAVIR score F3–F4	26% (54/207)	32% (66/205)
CD4 cell count >500	21% (43/207)	34% (70/205)
CD4 cell count <500	18% (37/207)	22% (45/205)

Peronne 2004

A preliminary analysis of histological responses indicated that virological responders had significant decreases in METAVIR scores (see Chapter IV, Diagnostics) for both fibrosis and disease activity (Perronne 2004).

The withdrawal rate in ANRS HC02 was shockingly high—43% of participants in each arm withdrew. Several factors may have contributed to the high discontinuation rate. A large proportion of ANRS HC02 participants had advanced liver disease (40%) and 17% had a history of an AIDS-defining condition; these people may have had difficulty tolerating simultaneous HAART and HCV treatment. Growth factors were not permitted for management of treatment-induced anemia or neutropenia, both of which may have led to withdrawals. Although it was unclear whether or not they were still active users, almost 80% of the study participants acquired HCV from injection drug use. No information is available regarding access to methadone or buprenorphine during this trial. Evaluating the contribution of current or former injection drug use to study discontinuations is not possible. Certainly, the importance of monitoring for, and managing side effects is underscored by discontinuations from ANRS HC02.

Common side effects in both treatment arms included flulike symptoms, weight loss, anxiety, insomnia, depression, hair loss and itching. At week 12, decreases in hemoglobin and platelets were significantly greater among those receiving pegylated interferon (-1.8 vs. -1.4 [P=0.002] for hemoglobin; -19,000 vs. -33,000 [P=0.031] for platelets), while decreases in neutrophil and absolute CD4 cell counts did not differ significantly by treatment arm. Severe adverse events were reported by 31% (127/ 410); 64 in the interferon arm and 63 in the pegylated interferon arm (Perrone 2004).

Table 11. Serious Adverse Events Reported in ANRS HC02 *

Adverse Events	
Psychiatric events	16
Sepsis	8
Pneumonia	7
Hepatic failure	4
Acute pancreatitis	5
Hyperlactatemia >5mM/l	6

Perronne 2002; Perronne 2004

*This is not a complete listing of serious adverse events from ANRS HC02.

An Uncontrolled Study of Pegylated Interferon Plus Ribavirin

Pérez-Olmeda and colleagues evaluated safety, efficacy and tolerability of HCV therapy in 68 coinfected individuals with CD4 cell counts of >300 and HIV RNA of <5000 (with or without antiretroviral therapy). Participants received a fixed dose of ribavirin (800 mg/day) with an induction dose of pegylated interferon alfa-2b. For the first 12 weeks of the study, they were given 150 μg per week. The dose of pegylated interferon was subsequently reduced to 100 μg per week until completion of therapy. For genotypes 1 and 4, the course of treatment was 48 weeks, for genotype 3, 24 weeks.

Table 12. Early Virological Response (EVR), End-of-Treatment Response and SVR According to Genotype

	EVR W 12	ETR W 24/48*	SVR W 48/72*
All	48.5% (33/68)	39.7% (27/68)	27.9% (19/68)
Genotypes 1&4	Not available	15% (10/68)	12% (8/68)
Genotype 3	Not available	81% (17/21)	52% (11/21)

Pérez-Olmeda 2003b

*ETR at 24 weeks for genotype 3. ETR at 48 weeks for genotypes 1 & 4

After controlling for other factors, the only significant predictor of achieving SVR was baseline HCV RNA <800,000 IU (OR, 5.5; 95% CI, 1.5–19.87; P=0.009).

Several factors contributed to low response rates. Doses of both drugs may have been suboptimal. For individuals weighing more than 75 kg, a higher dose of ribavirin is recommended if they can tolerate it (tolerability of ribavirin is a significant issue for HIV-positive persons, who often receive the 800 mg dose used in this trial). Based on the weight range of participants in this study, a quarter of the participants could have received a suboptimal dose of ribavirin, although the difference in response rates by ribavirin dose was not significant. Although pegylated interferon alfa-2b is dosed according to body weight, in this trial, it was given at two different fixed doses—150 μg per week for 12 weeks, then 100 μg per week until completion of treatment—regardless of body weight. The recommended dose for use in combination with ribavirin is 1.5 μg/ kg once weekly. The mean weight of participants in this study was 69 ± 11.2 kg. For the upper end of this weight range (80 kg), the recommended weight-based dose of pegylated interferon would be 120 μg; for the lower end of the weight range (58 kg), the recommended weight-based dose would be 87 μg. The post-induction dose (100 μg per week) may have been suboptimal for anyone weighing more than 66 kg. The rationale for this dosing scheme is unclear, and may have had a substantial impact on efficacy.

Although a 24-week course of treatment is recommended for genotype 2 or 3 in HCV moinfection, this may have been an insufficient duration of therapy for coinfected individuals with genotype 3. In this study, 30% of those with genotype 3 relapsed between the end of treatment and week 72. The authors suggested that the efficacy of treatment for coinfected people with genotype 3 may increase if treatment duration is extended to 48 weeks.

Fifteen percent of participants discontinued treatment due to adverse events. Some of the adverse events were unexpected, such as pancreatitis (N=1), asymptomatic hyperamylasemia (excess levels of amylase in the bloodstream) (N=4), and slightly elevated lactate levels (N=2). Both people with elevated lactate levels were taking stavudine (d4T; Zerit®). All of the individuals who experienced pancreatitis and asymptomatic hyperamylasemia were taking didanoisine (ddI; Videx®). These adverse events resolved after the discontinuation of therapy (Pérez-Olmeda 2003b). These and other data indicate that didanosine and stauvidine must be used cautiously, if at all, with ribavirin (see the section on drug interactions later in this chapter).

HCV Treatment Strategies For Coinfected People

Although the sustained virological response rates from APRICOT, ACTG A5071, ANRS HC02 and Pérez-Olmeda and colleagues were disappointing, these studies provide useful data and a path towards strategies for optimizing HCV treatment.

- **Identifying Prognostic Value of Baseline HCV RNA**

The prognostic value of baseline HCV RNA in coinfection is unknown. HCV viral loads are higher in coinfected people than those with HCV alone (Cribier 1995; Di Martino 2001; Eyster 1994; Sulkowski 2002; Thomas 2001; Zylberberg 1996). In HCV monoinfection, those with a low pre-treatment viral load (≤ 2,000,000 copies/mL or 800,000 IU) are more likely to achieve SVR. A different prognostic threshold may apply in coinfection. More information about likelihood of SVR according to baseline HCV RNA would be welcome.

- **Predicting SVR at Week 12**

Reports from APRICOT, ACTG A5071, ANRS and Pérez-Olmeda and colleagues concur: the virological response at week 12 has a negative predictive value of almost 100% in coinfected people, although the positive predictive value is not as robust (Chung 2004; Pérez-Olmeda 2003a; Perronne 2004; Torriani 2004). Other evidence supports the negative predictive value of the week 12 virological response in coinfected people. (Berenguer 2003b; Voigt 2003). Early, reliable prediction of treatment outcomes may support adherence among those who continue therapy, and spare non-responders from the side effects and expense of treatment.

- **Duration of Treatment for Genotype 2 or 3**

All participants in APRICOT, ACTG A5071, and ANRS HC02 were treated for 48 weeks, regardless of genotype. Extending treatment from 24 to 48 weeks for coinfected persons with genotype 2 or 3 decreased relapse rates in this group. Although there has not been a randomized, controlled trial comparing SVR rates in coinfected persons with genotype 2 or 3 by duration of treatment, the standard of care for this population may have already been redefined.

- **Extending Duration of Treatment in Genotype 1**

Perhaps using the same approach for improving treatment outcomes in genotypes 2 and 3—extending the duration of treatment—could increase efficacy in genotype 1. Some individuals with genotype 1 may be more likely to achieve SVR if duration of treatment is extended from 48 to 72 weeks. Further research is needed to identify those who are likely to achieve SVR by extending treatment.

- **Increasing Efficacy with Higher Doses of Ribavirin**

Using higher doses of ribavirin may increase treatment efficacy for coinfected people. Due to concerns about anemia in HIV-positive persons, the dose of ribavirin is usually 800 mg/day, regardless of weight. One HCV monoinfection trial reported more sustained virological responses

in individuals with HCV genotype 1 who received 1,000 to 1,200 mg/day of ribavirin than in those who received 800 mg/day (Hadziyannis 2004).

Hernández-Quero and colleagues are evaluating safety and efficacy of 48 weeks of pegylated interferon alfa-2a (180 mg/kg once weekly) with two doses of ribavirin (800 or 1,000 mg/day) among 149 coinfected people. So far, 108 have been treated for 24 weeks. Sixty-three percent (37/59) in the 1,000 mg arm had undetectable HCV RNA vs. 55% (27/49) in the 800 mg arm. With respect to genotype, 47.5% (28/59) with genotype 1, 84.4% (27/32) with genotypes 2 and 3, and 52.9% (9/17) with genotype 4 had undetectable HCV RNA at week 24. By week 24, 21 people had withdrawn from the trial; withdrawal rate did not differ by ribavirin dose. (Hernández-Quero2003). These results have not yet been broken out by both ribavirin dose and genotype. When the final data are available, the results must be evaluated specifically in genotype 1. Vigilant monitoring for, and prompt treatment of, anemia must accompany administration of high-dose ribavirin.

- **Decreasing Toxicity by Lowering the Dose of Pegylated Interferon**

Moreno and colleagues evaluated safety and efficacy of low-dose pegylated interferon plus ribavirin in 35 coinfected persons. All received 48 weeks of treatment with a fixed dose of 50 mg of pegylated interferon alfa-2b once weekly (the standard dose is 1.5 mg/kg once weekly) plus 800 mg/day of ribavirin. Overall, 31% (11/35) achieved SVR. The only significant predictor of SVR was genotype 2 or 3 (OR, 6.0; 95% CI, 1.1–31.7; $P<0.005$). SVR was achieved by 54% (7/13) with genotype 3, 21%(4/19) with genotype 1 and 0% (0/3) with genotype 4.

Although the response rates were comparable to those from ANRS HC02, decreasing the dose of pegylated interferon did not decrease side effects or adverse events. Ninety-one percent of the participants were receiving HAART during HCV treatment, which may have caused or exacerbated certain side effects of antiretroviral agents. Peripheral neuropathy developed in 9% (3/35), lactic acidosis in 6% (2/35) and weight loss of > 10kg (approximately 22 pounds) in 17% (6/35). An astounding 97% (35/35) reported flulike symptoms, while 40% (14/35) reported irritability and 9% (3/35) developed depression. Neutropenia developed in 60% (21/35) and anemia in 20% (7/35). Dermatological side effects (injection site reactions and dry and/or itchy skin) were common. Despite the adverse events, the discontinuation rate was fairly low (17%; 6/35) (Moreno 2004). Although data from this study do not warrant lowering the dose of pegylated interferon, it is encouraging that SVR rates—especially for genotype 1—did not differ significantly from those in ANRS HC02 or A5071.

- **Shifting the Treatment Paradigm**

For some coinfected people, the HCV treatment paradigm needs to shift from viral eradication to preventing additional liver damage. Long-term maintenance therapy with low-dose pegylated interferon may prevent HCV progression among HIV/HCV-coinfected people. This may be a viable option for those in whom SVR is unlikely, as well as for relapsers and virological non-responders. Maintenance therapy may stabilize liver disease until less toxic and more effective therapies are available. Two NIH-sponsored studies—one ongoing and another expected to open in late 2004—are evaluating safety and efficacy of maintenance therapy for coinfected virological non-responders.

Other Treatment Issues for Coinfected People

Drug Interactions

- **Ribavirin and Didanosine**

Cases of mitochondrial toxicity from the combination of ribavirin and nucleoside reverse transcriptase inhibitors (NRTIs) have been reported (Berenguer 2003a; Lafeuillade 2001; Pol 2003b; Salmon-Céron 2001; D. M. Smith 2002). A review of the Food and Drug Administration's Adverse Events Reporting System (AERS) revealed that combining didanosine with ribavirin was associated with a five-fold increase in the risk of mitochondrial toxicity-related events, such as pancreatitis, lactic acidosis with liver failure and/or hepatic steatosis. There were 65 unduplicated reports of adverse events in coinfected individuals receiving a combination of RBV and NRTI, and 26 of the 65 reported 53 events suggesting mitochondrial toxicity. Of these 26 individuals, 23 were taking didanosine and ribavirin. Three deaths occurred; two from liver failure, one from lactic acidosis and multi-organ failure (Fleischer 2003).

In September 2002, the FDA added a precaution about the co-administration of ribavirin and didanosine to the ddI label: "co-administration of ribavirin with VIDEX should be undertaken with caution, and patients should be monitored closely for didanosine-related toxicities. VIDEX should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develops" (Bristol Myers Sqibb package insert 2003). In vitro, ribavirin increases levels of ddI's active metabolite, dideoxyadenosine 5'-triphosphate (ddATP), which may exacerbate didanosine-related toxicities, including pancreatitis, symptomatic hyperlactatemia, lactic acidosis, and peripheral neuropathy.

- **Ribavirin and Stavudine**

Although there is no data on interactions between ribavirin and stavudine, some adverse events reported during HCV treatment trials indicate that the side effects and toxicities from stavudine may be exacerbated by concomitant ribavirin use (Moreno 2004; Pérez-Olmeda 2003b; Perronne 2002). Moreno and colleagues reported two cases of lactic acidosis during their study of HCV treatment in 35 coinfected individuals. Both were taking stavudine and one was also taking didanosine. Three cases of moderate or severe peripheral neuropathy developed during this study; all among people using stavudine. Peripheral neuropathy is a known side effect of stavudine (Dragovic 2003; Reliquet 2001). Changing HIV treatment regimens led to significant improvements in symptoms of peripheral neuropathy in all three people (Moreno 2004).

During their study of HCV treatment in 68 coinfected individuals, Pérez-Olmeda and colleagues reported that significant weight loss—averaging 4.5 kg or approximately 10 pounds—occurred within six months of initiating HCV treatment. The authors speculated that since almost half of the study participants were taking stavudine, their weight loss may have been attributable in part to side effects from stavudine, potentiated by concomitant ribavirin use (2003b). Didanosine and stauvidine must be used cautiously, if at all, with ribavirin.

- **Ribavirin, Interferon and Zidovudine**

Interferon induces anemia through bone marrow suppression, which is the same mechanism associated with anemia induced by zidovudine (AZT; Retrovir®) (Dieterich 2003; Glaxo Wellcome 2000). Ribavirin causes anemia via hemolysis (Bodenheimer 1997; Dieterich 2002b; Dusheiko 1996). Combining the two drugs increases the risk for anemia, because myleosuppression makes compensation for the loss of red blood cells difficult. Braü and colleagues reported an association between ribavirin, zidovudine and anemia in a study of HCV treatment in coinfected people. When ribavirin and zidovudine were used together, hemoglobin nadir levels were significantly lower (10.1 g/dL vs. 13.0 g/dL for ribavirin without concomitant zidovudine; P=0.001) and decreases in hemoglobin were significantly greater (-3.64 g/dL vs. –2.08 g/dL; P=0.002). Dose reduction for anemia was significantly more common among those using ribavirin and zidovudine (60% vs. 16% for no AZT; P=0.001) (Braü 2004a). Moreno and colleagues reported a significant association between development and severity of anemia and zidovudine use during an HCV treatment trial in coinfected persons (71% vs. 28% of stavudine users; P=0.021). In this study, all of the participants who developed moderate or severe anemia were receiving zidovidine (Moreno 2004).

- **IFN and Nucleoside Analogs**

Although the focus of research on interactions between antiretroviral agents and hepatitis C therapy has been on ribavirin, interferon may be involved as well. Anderson and colleagues have speculated that toxicities from nucleoside and nucleotide analogs may be potentiated by interferon. Interferon may upregulate phosphorylation of NRTIs via cellular activation. Evidence to support this comes from studies of NRTI phosphorylation in people with advanced HIV disease, when cellular immune activation is common. Greater rates of NRTI phosphorylation and more toxicities have been reported in persons with advanced HIV disease receiving NRTIs (Barry 1994; Fischl 1997; Hoggard 2001: Wattanagoon 2000). Although the increased toxicity of didanosine reported in people being treated simultaneously for hepatitis C and HIV has been attributed solely to ribavirin, interferon may contribute as well (Anderson 2004). If increased mitochondrial toxicity resulting from hepatitis C treatment can be demonstrated in people receiving NRTIs, then further drug-drug interaction studies examining interferon's role in potentiating NRTI-induced mitochondrial toxicity are warranted.

Side Effects of Hepatitis C Treatment in HIV-Positive Persons

The side effects of interferon and ribavirin may occur more frequently, and may be more severe in coinfected persons. People who are HIV/HCV-coinfected are more vulnerable for a number of reasons: treating HCV may induce or exacerbate HIV-related complications such as anemia and neutropenia, the potential for drug interactions increases when interferon and ribavirin are added to antiretroviral therapy and additional drugs added to ameliorate side effects of HCV treatment may add new side effects or cause new interactions. Although treatment of HCV and HIV may alleviate symptoms of each virus, the side effects from their treatments may be worse.

For additional information on the side effects associated with standard and pegylated interferon and ribavirin, see Chapter V, Hepatitis C Treatment, Management of Side Effects and Adverse Events.

- **Depression**

Depression is common among HIV-positive individuals, occurring in 20–80% (Tate 2003; Valente 2003). Major depression is not always identified in people with HIV. Asch and colleagues used the Composite International Diagnostic Interview survey to assess depression among 1,140 HIV-positive people, all of whom were receiving medical care. The survey results indicated major depression among 37% (448/1,140). When they compared the survey results to data on each individual's medical record, they found that 45% (203/448) had no documentation of depression in their medical records (Asch 2003). It is crucial to diagnose and treat depression in HIV-positive people, because depression is associated with decreased quality of life and an increased risk for HIV disease progression and death (Farinpour 2003; Tate 2003).

Depression is a known side effect of interferon (Koskinas 2002; Kraus 2003). Interferon-induced depression ranges in severity; attempted suicides have been reported in <1–2% of HCV mono-infection treatment trial participants (Roche package insert 2002; Schering package insert 2001). Myers and colleagues reported that treatment-induced depression was responsible for 50% (3/6) of withdrawals due to neuropsychiatric side effects in a an HCV re-treatment in 32 coinfected persons; one required hospitalization (Myers 2004). Laguno and colleagues identified depressive symptoms among 37% (40/109) of coinfected individuals during treatment with interferon and ribavirin. Four were hospitalized for severe depression and had to permanently discontinue HCV treatment. Seventeen were treated for depression with citalopram (Celexa™; a selective serotonin reuptake inhibitor), and reported significant improvement in depressive symptoms (Laguno 2003). The authors suggested pre-emptive treatment of depression as an intervention to decrease treatment discontinuations.

Assessment for depression prior to initiation of HCV therapy, monitoring during treatment, and intervention when indicated should be key elements of HCV treatment. Furthermore, research on strategies for managing interferon-induced depression is needed.

- **Anemia**

Anemia is of great concern to HIV-positive people. It occurs among 30% of asymptomatic individuals and up to 75–80% of persons with an AIDS diagnosis (Levine 2001). If anemia is untreated or does not respond to treatment, it is associated with more rapid HIV disease progression and death (Diallo 2003; Lundgren 2003; Mocroft 1999b; Moore 1998; Semba 2002; Sullivan 2002). Anemia is prevalent among HIV-positive women; risk for developing anemia increases with African-American race, age, use of zidovudine, and CD4 cell counts <200/mL (Levine 2001; Semba 2002; Sullivan 1998; Volberding 2004). Recombinant human erythropoietin (EPO) has been used successfully for treatment of anemia in HIV-positive individuals, improving quality of life as well as increasing survival (Miles 1992; Moore 1999; Moore 2000; Revicki 1994; Sullivan 2002).

The risk for anemia is especially significant for coinfected persons who are considering or undergoing HCV treatment. Interferon may cause anemia through suppression of bone marrow, and hemolytic anemia is a common, usually reversible side effect of ribavirin (Bodenheimer 1997; Dieterich 2002b; Dieterich 2003 Dusheiko 1996). Ribavirin may cause anemia more often in coinfected persons than in those with HIV alone (Dieterich 1999). The risk for ribavirin-induced

anemia increases with higher doses (Chang 2002). Dose reduction may decrease treatment efficacy (Sulkowski 2003d), so an additional strategy—treatment with epoetin-alfa (EPO; a synthetic version of a human protein that stimulates production of red blood cells)—has been studied for management of ribavirin-induced anemia in coinfected individuals (Weisz 2000; Golie 2003).

Golie and colleagues randomized 20/21 coinfected people who were being treated for HCV to two different interventions for ribavirin-induced anemia. When hemoglobin levels decreased to ≤ 10 mg/dl during treatment with pegylated interferon alfa-2b and ribavirin (13 ± 2 mg/kg per day), participants were randomized to RBV dose reduction (N=13) or treatment with EPO (N=7). The ribavirin dose was reduced to 10 mg/kg per day. Two weeks after dose reduction, 7/13 had mean hemoglobin increases from 8.9 mg/dl to 9.7 mg/dl (P=0.03). In the EPO group, within two weeks, 4/7 had increases in mean hemoglobin from 9.9 mg/dl to 11.4 mg/dl (P=0.02) (Golie 2003). This study was too small to evaluate the impact of each strategy on treatment outcomes. Larger studies are needed.

The largest decreases in hemoglobin usually occur within the first four to eight weeks of treatment with ribavirin. A complete blood count should be obtained at baseline, at two and four weeks after initiation of ribavirin (or more frequently if clinically indicated) and periodically during treatment (Roche package insert 2002; Schering package insert 2001).

- **Neutropenia**

Neutropenia often occurs in advanced HIV disease, and significantly increases the risk for, and incidence of bacterial infections (Kuritzkes 2000). Several studies have reported that recombinant human granulocyte-colony stimulating factor (G-CSF; Neupogen®) is an effective treatment for neutropenia in HIV-positive people (Hermans 1996; Kuritzkes 1998, Kuritzkes 2000; Mitsuyasu 1999).

Interferon induces neutropenia. In HCV monoinfection treatment trials, neutropenia has been associated more frequently with pegylated interferon than standard interferon (Fried 2002a; Manns 2001). A retrospective chart review of the incidence of neutropenia among coinfected HCV treatment trial participants reported a higher incidence of neutropenia (42%) than that seen in HCV monoinfection treatment trials (18–20%) (Fried 2002a; Manns 2001; Slim 2003). Reducing the dose of interferon may compromise the response to HCV therapy, so Golie and colleagues randomized 10 coinfected participants who developed neutropenia during an HCV treatment trial to dose reduction of pegylated interferon (N=3) or G-CSF (N=7). The pegylated interferon dose was reduced from 1.5 mg/kg per week to 1.0 mg/kg per week in one group; within two weeks, absolute neutrophil count increased from 553/mm^3 to 2013/mm^3 . In the other group of seven, who received 5 mg/kg of G-CSF twice weekly, absolute neutrophil counts rose from 571/mm^3 to 1814/mm^3 within two weeks (Golie 2003). No data on the response to HCV treatment were provided. Although this study reported that both interventions were effective for management of neutropenia, it is not possible to determine which intervention is preferable without HCV treatment response data.

- **Thrombocytopenia**

Thrombocytopenia (low platelets) is a common complication of HIV, especially in advanced disease (Louache 1994; Moses 1998; Scaradavou 2002). Thrombocytopenia has been associated with HCV infection, and occurs more frequently in persons with advanced liver disease (Pockros 2002; Ramos-Casals 2003). Interferon has been used to treat HCV-related thrombocytopenia, although it can also induce thrombocytopenia. In HCV monoinfection treatment trials, thrombocytopenia was reported more frequently with pegylated interferon than standard interferon (Fried 2002a). Dose modification or treatment discontinuation may be necessary if platelet counts drop markedly during HCV treatment.

- **Hemoglobinuria**

Hemoglobinuria (the presence of unbound hemoglobin in the urine, causing black or very dark urine) is a rare side effect of ribavirin (Diamond 2004; Massoud 2003). Because hemoglobinuria occurs with pronounced hemolysis, hemoglobin levels should be checked if hemoglobinuria develops.

- **Weight Loss**

Weight loss continues to be a significant problem for HIV-positive individuals in the HAART era (Wanke 2000). A weight loss of 5–10% from baseline has been associated with increased risk of developing opportunistic infections and death (Wheeler 1998; Wheeler 1999; Williams 1999). Nausea, vomiting, loss of appetite and weight loss are common side effects of interferon (Fried 2002b; Lindsay 2001; Manns 2001; Zeuzem 2000). Significant weight loss has been reported during HCV treatment trials in coinfected persons (Moreno 2004; Pérez-Olmeda 2003b; Pomova 2003).

Careful monitoring of weight loss during HCV therapy is recommended for coinfected persons. Possible strategies for management of weight loss include eating several small light meals throughout the day, and/or prescribing antiemetics or dronabinol (Marinol®).

- **Ocular Side Effects of Pegylated Interferon in Coinfected Persons**

A rare side effect of pegylated interferon is optic neuropathy, which may cause color blindness or complete loss of vision. In a study of 18 coinfected persons, one case of optic neuropathy was identified, two individuals developed cataracts and seven others developed cotton wool spots. Overall, ocular pathologies were observed in 39% (7/18) (Farel 2003). In many cases, the damage is reversible, but in some instances treatment may need to be temporarily or permanently discontinued to prevent partial or total loss of vision. Baseline assessment and vigilant monitoring for ocular problems, including color vision testing, are recommended.

HCV Treatment for Coinfected People with Hemophilia

A majority of the hemophiliacs who acquired HIV from clotting factors prior to 1985 (when viral inactivation procedures were instituted) also contracted hepatitis C. Coinfection with HIV is known to accelerate HCV progression in hemophiliacs and to increase their risk for developing end-stage liver disease (Goedert 2002; Lesens 1999; Ragni 2001).

The extent and severity of liver disease among coinfected hemophiliacs is difficult to assess unless clinical indications of advanced liver disease are present. Due to the risk for bleeding, liver biopsy is not routinely performed on hemophiliacs. Duration of HCV infection and liver enzyme levels before, during, and after HCV treatment are insufficient surrogate markers for assessing the severity of, and measuring improvements in HCV disease.

Data on safety and efficacy of standard interferon—with or without ribavirin—are available from few studies.

Table 13. HCV Treatment Efficacy In Coinfected Hemophiliacs: Interferon With or Without Ribavirin

Author	Regimen & Duration	N Participants	% SVR	Biological improvement	CD4 (mean)	Discont-inuations
Hanabusa 2002 Arm A: HIV/HCV Arm B: HCV	9 MIU of IFNa-2a once daily for 2 weeks, then 3 x week for 22 weeks 24 weeks total	Total N=30 Arm A: N=15 Arm B: N=15	Overall: 33.3% (10/30) Arm A: 33% (4/12) Arm B: 40% (6/15)	At end of treatment: Arm A: 50% (6/12) Arm B: 47% (7/15) At 2-year follow-up: Arm A: 58% (7/12) Arm B: 50% (7/14) At 4-year follow-up: Arm A: 100% (8/8) Arm B: 43% (6/14)	363 ± 29	Arm A: 20% (3/15) Arm B: 0% (0/15)
Sauleda 2001	3 MU IFNα-2b 3xweek; + 800 mg/day ribavirin after one month IFN monotherapy 24 weeks if HCV RNA was detectable; otherwise, 48 weeks	N=20	Overall: 40% (8/20) Genotypes 2&3: 80% (4/5) Genotypes 1&4: 27% (4/15)	Virological responders: 75% (6/8) had normalization of ALT during TX, and maintained normal ALT after TX. Virological non-responders: none had normalized ALT, but ALT levels decreased during and after TX.	490 ± 76	For toxicity: 0% For week 24 non-response: 60% (12/20)

Hayashi and colleagues studied the same interferon regimen used by Hanabusa and colleagues (9 MIU of IFNα-2a once daily for 2 weeks, then thrice-weekly for 22 weeks). They reported that 0/7 achieved a sustained virological response. A majority of participants in the Hayashi study had high levels of HCV RNA and/or low CD4 cell count, and most were receiving dual nucleoside therapy rahter than HAART (Hayashi 2000). These factors may have contributed to the disappointing response rate.

In March of 2002, a study sponsored by the National Institutes of Health (NIH) opened to evaluate the efficacy of pegylated interferon alfa-2a plus ribavirin in hemophiliacs with HCV and HIV/HCV coinfection, *Treatment of Hepatitis C in Hemophilic Patients with HIV*. The study is expected to conclude in mid-2005.

Treatment of Acute HCV in HIV/HCV Coinfection

Nelson and colleagues diagnosed acute hepatitis C infections in 49 HIV-positive men who have sex with men (MSM), and studied the outcome of both treated and untreated acute HCV infections. Due to the possibility of spontaneous viral clearance, it was suggested that treatment be delayed for 12 weeks (12/22 achieved spontaneous viral clearance during this period). Twenty-six men chose to be treated for HCV. All but four received pegylated interferon plus ribavirin. Three were treated with pegylated interferon, and one with interferon plus ribavirin. So far, 18 have completed treatment; ten have maintained undetectable HCV RNA during follow-up ranging from one to eight months. The only factor significantly associated with a virological response to HCV treatment was a higher peak ALT (482 vs. 177; P=0.021), although CD4 cell count, HIV and HCV viral load, HCV genotype, treatment regimen and the interval between diagnosis and initiation of treatment were also considered. The adverse events reported during treatment included depression, neutropenia, and flulike symptoms; one individual required a transfusion for anemia (Nelson 2003).

Vogel and colleagues treated eight HIV-positive individuals during acute hepatitis C infection. A majority had HCV genotype 1 (5/8). Five received pegylated interferon plus ribavirin, two received pegylated interferon and one received standard interferon. Of the eight, six (75%) achieved an SVR (Vogel 2003).

Different regimens and durations of treatment for acute HCV infection in HIV-positive people merit further investigation.

Retreatment of HCV in HIV/HCV Coinfected Individuals

Rodriguez Torres and colleagues studied the efficacy of HCV re-treatment in a group of 76 coinfected non-responders to interferon with or without ribavirin. Participants were randomized to receive pegylated interferon alfa-2a with or without 800 mg/day of ribavirin for 24 weeks. At week 24, individuals who did not have a decrease of ≥ 2 $\log_{10}$ in HCV RNA discontinued treatment. Virological responders who received pegylated interferon monotherapy added 800 mg/day of ribavirin at week 24. Sustained virological responses were achieved by 5.7% (2/35) of those initially randomized to pegylated interferon monotherapy vs. 19.5% (8/41) of those randomized to pegylated interferon plus ribavirin. SVR rates were not broken out by baseline HCV RNA or HCV genotype.

More than a quarter (20/76) discontinued treatment. There were more withdrawals from the pegylated interferon monotherapy arm than the combination therapy arm (15 and 5, respectively). Discontinuations were attributed to lost-to-follow-up (9/20), adverse events (7/20) and laboratory abnormalities (4/20). Overall, laboratory abnormalities occurred more frequently among those on combination therapy (26/41) than pegylated interferon monotherapy (13/35) (Rodriguez-Torres 2003).

Myers and colleagues re-treated 32 coinfected people who relapsed (N=6) or did not respond (N=26) to previous HCV therapy (interferon with or without ribavirin). Participants received 24 weeks of pegylated interferon alfa-2b (median dose 1.0 μg/kg once weekly; range: 0.5–1.5 μg/kg) and ribavirin (median dose of 1,000 mg/day; range: 600–1,200 mg/day). Those with detectable

HCV RNA discontinued treatment at 24 weeks (34% or 11/32), while those with undetectable HCV RNA continued treatment for an additional 24 weeks.

SVR was achieved by 16% (5/32). The small sample size—and consequently, the smaller number of sustained virological responders—make it difficult to identify any significant predictor of a SVR, although there were non-significant trends associated with achievement of an SVR (non-1 genotype, lower baseline HCV RNA [5.32 ± 0.93 vs. 6.16 ± 0.79 $\log_{10}$], higher CD4 cell count [580 ± 172 vs. 460 ± 211/mL] and higher ALT [139 ± 37 vs. 96 ± 68 IU/l).

Most participants (94%) were receiving antiretroviral therapy during HCV treatment. Six people changed antiretroviral regimens during HCV treatment due to increasing HIV RNA or decreasing CD4 cell counts (N=4), anemia (N=1) and diarrhea (N=1). Although 78% (N=25) experienced decreases in absolute CD4 cell count (median –135/ml; range: -441 to + 16//ml), their CD4 cell counts returned to baseline by week 36. Both CD4 cell percentage and HIV RNA remained stable during treatment.

The withdrawal rate in this study was quite high (47%), and can be attributed to both virological non-response and side effects. Fourteen participants cited side effects rather than virological non-response as their rationale for treatment discontinuation (depression, anxiety, agitation and delirium [N=6]; fatigue, insomnia and weight loss [N=6]; neutropenia and thrombocytopenia]N=2]), while one person withdrew because of hepatocellular carcinoma (Myers 2004).

Strategies to optimize re-treatment of coinfected relapsers and non-responders are needed.

HCV Treatment in Coinfected Cirrhotics

A small study evaluated the safety and efficacy of 24 weeks of standard interferon alfa-2b plus ribavirin in six coinfected cirrhotics. All six participants had been on stable antiretroviral therapy for at least two months before they started HCV treatment. Four of the six received 6 MU of interferon thrice weekly; the other two participants received 3 MU thrice weekly. All received 1000–1200 mg/day of ribavirin. Although 5/6 had an end-of-treatment response, only 2/6 had a sustained virological response. No hepatic decompensations or other severe adverse events were reported (De Bona 2002).

In ANRS HC02, 39% of participants had advanced fibrosis or cirrhosis. When sustained virological response rates were broken out by liver histology, the response rates did not differ significantly according to the degree of liver damage. In the pegylated interferon arm, 25% (51/205) of those with a METAVIR score of F0–F2 achieved SVR, while 32% (66/205) of those with F3–F4 achieved SVR (Perronne 2004).

Liver Transplantation in HIV-Positive People

The United Network for Organ Sharing (UNOS) policy on transplantation for HIV-positive transplant candidates states,

> A potential candidate for organ transplantation whose test for HIV-Ab is positive but who is in an asymptomatic state should not necessarily be excluded from candidacy for organ transplantation, but should be advised that he or she may be at an increased risk of morbidity and mortality because of immunosuppressive therapy.

The UNOS policy was last revised on June 24th, 1992—prior to the era of highly-active antiretroviral therapy. UNOS does not govern the policy on transplantation in HIV-positive candidates at individual transplant centers, but an updated policy would certainly contribute to greatly needed efforts towards broader access to transplantation for HIV-positive people. A survey of 148 directors of transplantation at renal transplant centers was released in 1998. Eighty-eight percent of survey respondents would not transplant a kidney from a cadaveric donor, and 91% would not transplant a kidney from a living donor into a person with asymptomatic HIV infection who was otherwise a good candidate for transplantation. A majority of centers reported a fear of transplantation in HIV-positive individuals; some believed that transplantation into HIV-positive persons was "a waste of precious organs" (Spital 1998). The reluctance to perform organ transplantation in HIV-positive people may persist, despite substantial data on the clinical and immunologic benefits of antiretroviral therapy (Palella 1998; Hogg 1999; Sendi 1999). Clearly, research on patient and graft survival in HIV-positive transplant recipients is needed.

Post Transplantation Survival Before the HAART Era

Before antibody screening for HIV was developed, some organ recipients contracted HIV via organs or blood transfusions from infected donors, while others who were infected prior to transplantation were not diagnosed until after transplantation. Before HAART, HIV treatment was not potent enough to control HIV disease progression for long periods of time in many individuals. Lack of effective treatment for HIV reduced post-transplant survival of some HIV-positive organ recipients. Bouscarat and colleagues followed eleven liver transplant recipients who were infected from 1985 to 1987, during or after transplantation. The seven-year post-transplantation survival rate was 36% for HIV-positive organ recipients vs. 70% for HIV-negative transplant recipients (Bouscarat 1994). A study of transplantation in 15 HIV-positive adults followed between 1981–1988 reported that AIDS was the leading cause of death; 5/15 died during a follow-up period ranging from 0.7–6.6 years (Tzakis 1990).

Erice and colleagues studied 88 HIV-positive organ recipients. The mean time for progression to AIDS after transplantation was 27.5 months. Individuals who were HIV-negative before transplantation did not progress to AIDS as quickly as those infected prior to transplantation, despite the use of immunosuppressive agents (32 months vs. 17 months) (Erice 1991).

There has been much concern about the effects of immunosuppressive therapy in HIV-positive persons, yet encouraging data on one immunosuppressive agent—cyclosporine—has emerged from the pre-HAART era and from more recent research on a potential role for cyclosporine as an

adjunct to HAART in primary HIV infection (Rizzardi 2002). Dummer and colleagues performed a retrospective analysis of data from 1,043 transplant recipients, 18 HIV-positive. After a mean interval of 43 months, 50% (9/18) of the HIV-positive organ recipients were still alive, suggesting that immunosuppressive therapy with cyclosporine did not exacerbate HIV disease (Dummer 1989). Schwarz and colleagues evaluated the medical records of 53 renal transplant recipients, who contracted HIV from infected organ donors. The five-year cumulative incidence of AIDS was significantly lower in the 40 individuals who had received an immunosuppressive regimen containing cyclosporine than that of 13 individuals who did not receive cyclosporine (31% vs. 90%; P=0.001) (A. Schwarz 1993).

Transplantation in the HAART Era

As HAART has brought significant clinical benefits for people with HIV disease, HCV- related end-stage liver disease has become a leading cause of death among people with HIV (Bica 2001; Martín-Carbonero 2001; Monga 2001; Quintana 2002). Thus, an increasing number of HIV-positive transplant candidates with end-stage liver disease have an urgent need for a transplant. Promising reports of post-transplant survival in HIV/HCV coinfected liver recipients have come from transplantation centers in Miami, Pittsburgh, San Francisco and Paris (Neff 2003c; Ragni 2003a; Ragni 2003b; Roland 2003; Samuel 2003).

Table 14. Survival Rates at One Year After Liver Transplantation

Source	Population	Survival Rate
Organ Procurement & Transplantation Network 2002	HIV-negative, from living donor	85.2%
	HIV-negative, from deceased donor	86.3%
Roland 2003	HIV/HCV or HBV coinfected from UCSF	79% (16/19)
Neff 2003c	HIV/HCV or HBV coinfected from UM	100% (6/6)
	HIV/HCV or HBV coinfected from UPMC	90% (9/10)
	Overall from UM and UPMC	94% (15/16)
	HIV/HCV coinfected liver recipients from UM and UPMC	90.0%(10/11)
Samuel 2002	HIV/HCV coinfected from Hôpital Paul Brousse, France	85.7% (6/7)

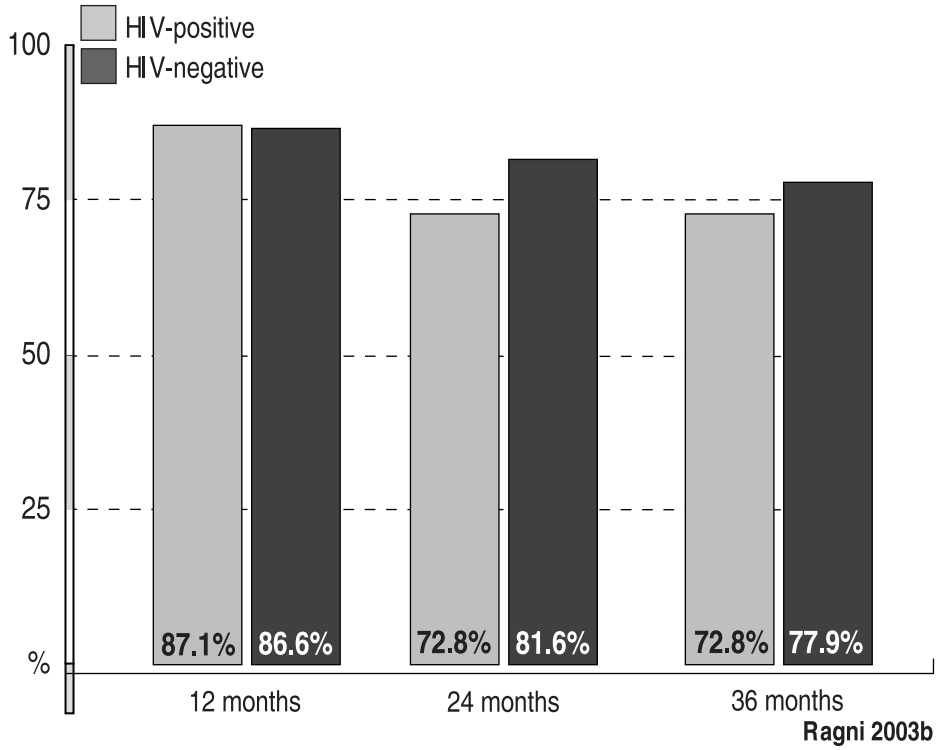
UM = University of Miami; UPMC = University of Pittsburgh Medical Center

A retrospective analysis of the outcomes of liver transplantation in the HAART era reported on CD4 cell counts, HIV RNA and graft survival among 19 HIV-positive liver recipients. During a follow-up interval ranging from 3–1696 days (median: 314 days), four deaths occurred. They were caused by recurrent HCV (N=1), rejection resulting from drug interaction (N=1), post-operative pancreatitis (N=1) and sinus thrombosis 4.5 years after transplantation (N=1). CD4 cell counts were stable, and most people had undetectable HCV RNA. The rate of graft rejection during follow-up was 21%, which is similar to the UNOS rejection rate in HIV-negative individuals (Roland 2003).

Ragni and colleagues reported survival data at one, two and three years after liver transplantation among 24 HIV-positive transplant recipients, 15 HCV coinfected. Post-transplant antiretroviral

intolerance developed in 40% (6/15) of the coinfected liver recipients, four of whom died. All four developed recurrent HCV, and were being treated with interferon and ribavirin. The remaining two resumed antiretroviral therapy.

Figure 8. Survival Rate at 12, 24 and 36 Months After Transplantation by HIV Status



Survival was significantly associated with the post-transplant CD4 cell count and HIV RNA. Survival after transplantation was significantly poorer among those with a post-transplantation CD4 cell count of <200 cells/μL and an HIV RNA >400/mL (P=0.005 and P=0.016, respectively). Thus, the authors suggest that survival may be predicted more accurately by the virological and immunological responses to antiretroviral therapy before end-stage liver disease (ESLD). ESLD may make it impossible for some candidates to tolerate HAART, so using pre-transplant CD4 cell count and HIV RNA as the sole eligibility criteria may unnecessarily disqualify good candidates.

Survival was significantly poorer among the 15 HCV-coinfected liver recipients (P=0.023) than those with HBV/HIV-coinfection (N=7) and HIV-positive persons transplanted because of fulminant liver failure (N=3). However, post-transplantation survival of coinfected transplant recipients did not differ significantly from that of persons with HCV monoinfection (Ragni 2003b). The sample size was small; data from larger groups of coinfected transplant recipients are needed.

A review of data from eleven HIV/HCV coinfected patients who had liver transplants at the University of Miami (UM) and the University of Pittsburgh (UP) between September of 1997 and December of 2001 reported that ten of the eleven transplant recipients maintained undetectable HIV RNA levels during follow up. Prior to transplantation, all had CD4 cell counts of <200; these have increased to >200 after transplantation (Neff 2003c).

Nowak and colleagues studied outcomes of four coinfected liver transplant recipients. They reported that HIV RNA was controlled, and CD4 cell counts increased when HAART was reinitiated after transplantation. One of the four had a primary HIV infection after transplantation; in this individual, HIV RNA decreased during the second week after infection, despite immunosuppressive therapy. By the third week, HIV RNA began to increase, and antiretroviral therapy was started. All four individuals maintained undetectable HIV RNA. One individual died at three months, while the other three were alive at three months, nine months and three years after transplantation (Nowak 2003).

Rufi and colleagues are conducting a prospective cohort study evaluating safety and efficacy of liver transplantation in HIV-positive persons. So far, six sites have performed liver transplants in 21 HIV-positive people, 19 HCV-coinfected. All received antiretroviral therapy before transplantation, when the median CD4 cell count was 247/mL (range: 110–589) and almost all (95%) had undetectable HIV RNA. All initiated antiretroviral therapy within a median of 5 days (range: 3–30) after transplantation. Only one person experienced immunological progression of HIV disease (CD4 count <100/mL) after transplantation.

Table 15. CD4 Cell Count and HIV RNA After Liver Transplantation

Timepoint and number	CD4 cell count/ mL median (range)	HIV RNA <200 copies/mL
Prior to transplantation (N=19)	247 (110–589)	95%
1 month after transplantation (N=19)	228 (119–564)	88%
3 months after transplantation (N=16)	250 (130–462)	86%
6 months after transplantation (N=12)	216 (154–480)	100%
12 months after transplantation (N=5)	253 (165–440)	100%

Rufi 2004

Although there were eight cases of acute graft rejection, none required re-transplantation. Recurrent HCV was cited as the major concern; it developed among 75% (15/19), appearing between 1–12 months after transplantation. Almost half (47%) are being treated with pegylated interferon plus ribavirin. Two transplant recipients have died: one at three months from sepsis and one from cirrhosis resulting from recurrent HCV at 14 months (Rufi 2004).

Treatment of Recurrent HCV

The need for effective HCV treatment after transplantation was underscored by a report from King's College Hospital in London. All four HIV/HCV coinfected liver recipients survived transplantation, although HCV recurred. Two of the four were treated with interferon and ribavirin, yet all four died from HCV-related complications between 3–25 months after transplantation (Boyd 2001).

Reports of treatment outcomes from Miami and Pittsburgh have been more encouraging. In Miami, two of three coinfected liver recipients developed recurrent HCV. Both were treated with pegylated interferon alfa-2b plus ribavirin. Although HCV treatment did not result in SVR for either individual, one had a reduction in inflammation and the other had reductions in both inflammation

and HCV RNA levels. Five of six HIV/HCV coinfected liver recipients in Pittsburgh developed recurrent HCV. One individual experienced graft rejection after the physician discontinued treatment with a protease inhibitor without making a corresponding adjustment to the dose of his immunosuppressive therapy; then, the treatment for graft rejection was complicated by recurrent HCV. The patient developed renal failure and died 19 months after transplantation. One of the remaining four was not been treated for HCV, because a biopsy showed no evidence of hepatitis. The other three individuals have been treated with interferon and ribavirin. One achieved SVR and the other two have had normalization of liver function tests while undergoing HCV treatment (Neff 2003c).

Aside from the pressing clinical need for better data and more access to transplantation for coinfected individuals, transplantation also presents an opportunity for immunologic and pharmacokinetic research. The effects of two immunosuppressive agents—cyclosporine and mycophenolate mofetil—on HIV disease, and the potential for synergistic as well as dangerous interactions with these drugs and certain antiretrovirals merit further investigation. The case histories of coinfected transplant recipients generate numerous clinical management issues: prevention and reversal of graft rejection, selection of antiretrovirals, proper dosage of immunosuppressive agents, the incidence and management of opportunistic infections in the milieu of immunosuppression, especially those for which there is no prophylaxis (Kaposi's sarcoma and human papilloma virus). The efficacy and tolerability of treatment for recurrent hepatitis C is a crucial issue. The National Institutes of Health has funded the *Kidney and Liver Transplantation in People with HIV Study*, a prospective, multi-center cohort study of 275 HIV-positive kidney and liver recipients, who will be followed for two to five years. It opened in late 2003.

Drug Interactions: Protease Inhibitors and Immunosuppressants

Drug-drug interactions are a significant concern for coinfected liver transplant recipients and their medical providers. There are significant interactions between protease inhibitors and the immunosuppressive agents used after transplantation to prevent graft rejection. A two-year evaluation of interactions between antiretrovirals and cyclosporine in 22 HIV-positive transplant recipients reported that cyclosporine increased or decreased the area under the curve (AUC) of protease inhibitors, while the AUC of NNRTIs remained close to levels seen in published studies. Pharmacokinetic studies were performed prior to transplantation, during weeks 1, 2, 4, 8, 12, 28, 52, 104, and if antiretroviral therapy was changed. The dose of cyclosporine needed progressive reduction in individuals taking protease inhibitors with or without NNRTIs, due to the increasing intestinal bioavailability of cyclosporine that occurs over time (Frassetto 2003).

Significant interactions between tacrolimus (another immunosuppressant), and protease inhibitors — especially lopinavir/ritonavir (Kaletra®) and nelfinavir (Viracept®)— have been reported (Jain 2002b; Jain 2003; Schvarcz 2000; Sheikh 1999). Jain and colleagues reported that lopinavir/ritonavir significantly increased tacrolimus levels in three coinfected liver transplant recipients. In one individual, tacrolimus dosing was adjusted from 5mg twice daily to 0.5 once weekly after introduction of lopinavir/ritonavir. In another, the area under the curve (AUC; a measurement of the amount of a drug that reaches the bloodstream during a specific period of time) for tacrolimus increased from 31 ng/mL/h to 301 ng/mL/h after lopinavir/ritonavir was introduced. They recommended using "great caution" when adjusting tacrolimus dosing at initiation and

discontinuation of lopivavir/ritonavir (Jain 2003). The interaction between tacrolimus and nelfinavir was crudely demonstrated when a transplant recipient discontinued nelfinavir without a concomitant adjustment in tacrolimus dosing; this led to graft rejection, renal failure and eventual death (Neff 2003c). Jain and colleagues studied interactions with protease inhibitors and tacrolimus in six liver transplant recipients (one of whom received indinavir; the other five, nelfinavir-based regimens). They compared tacrolimus dosing in the six HIV-positive liver recipients on HAART to that of HIV-negative transplant recipients. The proper dose of tacrolimus in nelfinavir-using liver transplant recipients was determined to be 38 times lower than the regular dose (Jain 2002b). A case report of the interaction between tacrolimus and protease inhibitors (saqinavir [Fortovase®], ritonavir [Norvir®], and nelfinavir) in one individual found that tacrolimus dosing had to be decreased by >95% when administered with nelfinavir (Sheikh 1999). An interaction between sirolimus (a newer immunosuppressant) and nelfinavir has been identified in a case report, where sirolimus levels were five to nine times higher in an individual who was also taking nelfinavir (Jain 2002c).

MELD (Model for End-Stage Liver Disease) Scoring: Impact on HIV-Positive Transplant Candidates

The Model for End-Stage Liver Disease (MELD) system is used to evaluate transplant candidates; MELD replaced the Child-Pugh Score in February of 2002 (see Chapter IV, Diagnostics). The MELD system is regarded as the most accurate and objective method of identifying those with the most urgent need for liver transplantation within a three month period and prioritizing them on the waiting list, thus decreasing the mortality rate among transplant candidates (Kamath 2003).

The MELD allocation system may extend the wait for organs among HIV-positive transplant candidates. More data is needed before the effect of the MELD system on HIV-positive transplant candidates can be evaluated. The need for transplantation may be more urgent among coinfected candidates with hepatic decompensation. A retrospective chart review analyzed survival among 41 coinfected individuals with decompensated cirrhosis, reporting that the median survival time after development of ascites was 123 days; the probability of survival at six months was 38% (Von Wichmann 2003b). In HCV monoinfection, the survival rate at five years after hepatic decompensation is 50% (Fattovich 1997).

Access to transplantation does not depend solely on an individual's MELD score. Organs are allocated regionally. The MELD score at which a candidate receives a transplant may vary, depending on the availability of organs and the number of other candidates in a particular region. Candidates with high MELD scores and the most urgent need for a transplant may be less likely to survive transplantation than those with less immediate need. This is mainly due to a chronic shortage of donor organs. Because of this shortage, the MELD system may have a negative impact on overall survival of transplant candidates, regardless of their HIV status.

A retrospective comparison of the MELD scores of transplant recipients with hepatitis C prior to and after the implementation of the MELD system did not find any significant differences in allocation for transplantation. Before the MELD system was adopted, the mean MELD score in transplant recipients was 19 (range: 11–35). After implementation of the MELD system, the mean MELD score in transplant recipients was 17.2 (range: 7–31). There were no differences in

allocation by gender, or allocation by MELD score over a period of one, two and three months before transplantation. The investigators did identify a trend towards increased transplantation of individuals with HCV-related hepatocellular carcinoma after the implementation of the MELD system (Meyer 2003).

The impact of the MELD allocation system on overall post-transplant survival rates—particularly on survival of HIV-positive liver recipients—needs evaluation.

Access to Transplantation

Limited supply of organs, a fragmented transplantation system, and financial coverage for transplants are all critical for HIV/HCV coinfected individuals. Many insurers consider it to be an experimental procedure and have declined coverage. An experimental designation should not apply to an established procedure simply because a candidate is HIV-positive.

Other Factors Affecting Treatment and Survival of Coinfected Persons

HCV antibody status may be serving as a marker for poorer access to care and competing problems with addiction that lead to delays in care or failure to implement the standard of care…if we are to improve the health status of patients with HIV-HCV coinfection, perhaps we should focus on these issues as well as the presence of the 2 viruses.

—C. S. Graham
Clinical Infectious Diseases

Presenting With Advanced HIV (and HCV) Disease and Limited Access to Care

The number of people diagnosed with AIDS immediately after their HIV diagnosis reflects limited access to care among people who are at high risk for HCV coinfection. HIV and AIDS surveillance data collected from 25 states during the period from 1994–2000 found that 26% (33,144/128,813) of those who were diagnosed with HIV already had AIDS. Twenty-four percent of this group (7,955/33,144) acquired HIV from injection drug use (CDC 2002c). Since HCV is widely prevalent among IDUs, it is safe to assume that a majority of these 33,144 individuals are coinfected.

Coinfected individuals may receive HAART significantly later, or at lower baseline CD4 cell counts than those with HIV monoinfection, despite evidence of the clinical benefits of HAART in people who are coinfected (Hare 2002; Sulkowski 2002; Tedali 2003a; Tedali 2003b; Torriani 2001; Qurishi 2002a; Qurishi 2002b). The delay in initiation of HAART may be attributed to several factors that also have an effect on survival: limited access to care, injection drug use and poverty. For example, individuals from lower socioeconomic strata are less likely to be prescribed triple-combination therapy regardless of clinical indications (Mc Farland 2003; Wood 2002).

Ineligibility for HCV Treatment

Until recently, active drug use has been a contraindication for HCV treatment. Although interferon has not been expressly contraindicated in people with psychiatric co-morbidities, many have traditionally been considered ineligible for HCV treatment. HIV and HCV are common among individuals with mental illness and/or drug addiction (Bolumar 1996; Marsh 2002; Meyer 2003; Rohrig 1990; Schmitt 1994). Rosenberg and colleagues screened 931 individuals receiving treatment for severe mental illness in Connecticut, Maryland, New Hampshire and North Carolina for HIV and HCV. They reported that HIV prevalence in this group was approximately eight times greater than that of the general population (3.1% vs. 0.335%) and HCV prevalence was approximately eleven times greater (19.6% vs. 1.4%) than that of the general population (Rosenberg 2001).

In a clinic at Chicago's Cook County Hospital, Soto and colleagues screened 241 HIV-positive adults with and without psychiatric co-morbidities (including addiction to drugs/alcohol) for HCV antibodies. Participants were grouped by the presence or absence of psychiatric co-morbidities and addiction. The overall prevalence of HCV was 28%. HCV was far more prevalent among individuals with psychiatric co-morbidities and addiction (40% vs.14.6% for individuals without a psychiatric or addiction diagnosis) (Soto 2002).

These significant co-morbidities have resulted in reduced eligibility for HCV treatment among a significant proportion of coinfected individuals (Bini 2004; C. A. Fleming 2003; Jarousse 2002; Restrepo 2003; Schwartzapfel 2002; L. E. Taylor 2002).

Bini and colleagues assessed eligibility for HCV treatment in a cohort of 280 coinfected people. Eligibility for treatment was established by combining well-known inclusion and exclusion criteria with the treating clinician's assessment. Coinfected people were considered significantly less likely to be eligible candidates for HCV treatment by both parameters than those with HCV monoinfection (P=0.01 according to exclusion criteria; P=0.02 according to clinician opinion). Predictors of treatment ineligibility according to clinician opinion were: ongoing or recent substance abuse (OR, 26.0; 95% CI, 5.2–128.8), co-morbid medical conditions (OR, 19.4; 95% CI, 6.4–58.9), albumin <3.2 g/dl (OR, 15.2; 95% CI, 1.5–157.2), psychiatric co-morbidity (OR, 5.7; 95% CI, 1.2–26.6), and annual income of <$10,000 per year (OR, 2.6; 95% CI, 1.0–6.4) (Bini 2004).

Fleming and colleagues evaluated eligibility for HCV treatment in a cohort of 149 coinfected persons. Only 29% (44/149) met the criteria for treatment eligibility.

Table 16. Reasons for HCV Treatment Ineligibility

Cause of Treatment Ineligibility	% (N=105)
Non-adherence to medical visits	23% (24/105)
Drug/alcohol use during previous six months	23% (24/105)
Active psychiatric disease	21% (22/105)
Advanced HIV disease	13% (14/105)
Decompensated liver disease	12% (13/105)
Medical comorbidities	8% (8/105)

C. A. Fleming 2003

Of those eligible for HCV therapy, 64% (28/44) chose not to undergo treatment (C. A. Fleming 2003).

Table 17. Reasons for HCV Treatment Refusal

Cause of Treatment Refusal	% (N=28)
Concern about potential side effects of HCV treatment	31% (9/28)
Did not return for treatment	21% (6/28)
Relocated	11% (3/28)
Concern about ability to work during treatment	11% (3/28)
Unstable social circumstances	11% (3/28)
Concern about relapse to active injection drug use	7% (2/28)
Pregnancy of partner	3.5% (1/28)
Death by unrelated cause	3.5% (1/28)

C. A. Fleming 2003

Taylor and colleagues investigated low enrollment of coinfection clinic patients in an HCV treatment trial. They reported that a majority of patients were ineligible due to medical contra-indications (58%), psychiatric illness (26%), active drug use (20%), and previous HCV treatment (6.5%); the remaining 26% did not choose to participate in the study (reasons not specified) (L. E. Taylor 2002). Another evaluation of 231 coinfected patients found that only 24% (56/231) were eligible for HCV treatment. Reasons for HCV treatment ineligibility included alcohol consumption of more than 30 grams per day (43/231), severe mental illness (28/231), and active injection drug use (6/31) (Von Wichmann 2003a).

These considerable barriers to care will only be surmounted by outreach initiatives to underserved and at-risk populations. Outreach initiatives must be linked to medical and mental health providers, drug and alcohol treatment programs and methadone maintenance facilities.

Multidisciplinary Care

Encouraging results have emerged from a pilot program for treating HCV in HIV-positive individuals with co-morbid mental illness and/or addiction. In a Rhode Island clinic, Schwartzapfel and colleagues evaluated 38 coinfected individuals, 95% of whom had a history of addiction and 84% of whom had a history of mental illness. Liver biopsy was performed in 23, revealing that eight had stage 3 fibrosis and six were cirrhotic; three developed decompensated liver disease during the evaluation process. Based on the urgent need for treatment, individualized care plans were developed with a team including an HIV specialist, a gastroenterologist, a psychiatrist, a nurse and an outreach worker who made frequent contact with those undergoing HCV treatment. The first two individuals who received HCV treatment and care from this multidisciplinary team have had virological responses to treatment without serious adverse events (Schwartzapfel 2002).

Hepatitis C Treatment in Coinfected Injection Drug Users

Little is known about HCV treatment outcomes or side effects in coinfected injection drug users, as they have often been excluded from clinical trials, or so few have participated that it is impossible to determine this information. Clearly, research on treatment of coinfected active injection (and non-injection) drug users is a priority.

Impact of Repeated Exposure to HCV From Injection Drug Use on Efficacy of HCV Treatment

Since injection drug users may be repeatedly exposed to HCV, it has been suggested that the low rates of virological response to HCV treatment among coinfected people might be partially attributable to infection with more than one genotype of HCV. Hypothetically, since HCV-genotypes 2 and 3 are more sensitive to treatment than genotypes 1 and 4, an initial viral clearance of an HCV genotype 2 or genotype 3 infection might allow a shift to a masked infection with a more treatment-resistant genotype. Soriano and colleagues examined this possibility in a group of 30 coinfected former IDUs. Ten of these individuals had HCV genotype 3; although they initially cleared HCV, while still on treatment, their virus became detectable. A comparison of baseline and post-treatment genotypic results revealed no difference in HCV subtypes (Soriano 2003).

Issues Concerning Medical Care and Treatment of Injection Drug Users

> *As someone who was closely involved in the original (illegal) efforts to establish needle exchange in New York City and having worked in one position or another as an advocate for the health care needs of illicit drug users for the past ten years, I was intimately aware of the incredible stigma, discrimination, and outright hostility and disgust injection drug users routinely face when attempting to seek health care services of any kind. Suddenly, I was my own client, and all those years I'd spent advocating for other drug users, while giving me insight into some of the systems I would now have to negotiate for myself, did not prepare me for the treatment I would also receive as a heroin injector with AIDS.*
>
> —I. Thaca
> *Harm Reduction Communication*

> *I felt my GP's diagnosis was not that I had a serious liver disease, but an untreatable moral malady.*
>
> —Lisa Waller
> *Medical Journal of Australia*

Injection drug use was identified as the mode of transmission by 21% (21,469/101,881) of people diagnosed with HIV from 1999 through 2002 (Glynn 2004). According to the Centers for Disease Control, injection drug use directly and indirectly accounts for 36% of AIDS cases in the United States (CDC 2002e). Up to 90% of people who acquired HIV from injection drug use with unsterilized equipment are coinfected with hepatitis C (CDC 2002f). The needs of coinfected

active and former injection drug users must be addressed by clinicians and incorporated into medical care and treatment.

Even in the HAART era, injection drug use remains linked with an increased risk for progression to an AIDS-defining condition or death in HIV-positive and HIV/HCV coinfected persons (Egger 2002: Voirin 2003; Schlanger 2004). An analysis of data from a cohort of 3,547 HIV-positive individuals collected during 1990–1995 and 1996–2000 revealed that injection drug users derived less disease-free survival time from HAART than non-IDUs. HAART increased disease-free survival time for non-IDUs with <200 CD4 cells by 135% vs. 34% for IDUs with <200 CD4 cells (Poundstone 2001). From 1996 until 2002, Voirin and colleagues found that the risk of death among 1,470 HIV-positive people did not differ significantly by HCV status (HR 0.76; 95% CI, 0.28–2.08; P=0.59). Injection drug use increased the risk of death for coinfected persons. Coinfected IDUs had a significantly greater risk than that of HIV-positive or HIV/HCV coinfected non-IDUs (HR 2.92; 95% CI, 1.63–5.23; P<0.001) (Voirin 2003). In New York City, HCV-related death rates increased among coinfected IDUs from 0.3% in 1993 to almost 4% in 1999. HCV-related liver disease was the leading cause of death among coinfected IDUs (79.2% vs. 50.2% for other causes of death; P<0.0001) (Schlanger 2004).

The institutional norms and stigma associated with injection drug use have created considerable barriers to care and treatment for people with HIV and hepatitis C. Until 2002, active injection drug use was a contraindication for treatment of hepatitis C, and many physicians still consider it to be one. Barriers to treatment for injection drug users are reflected in several reports of HIV-positive injection drug users who have not received HAART, or have initiated HAART later than non-drug users (Bassetti 1999; Bogart 2000; Maisels 2001; Mocroft 1999a; Murri 1999).

Physicians have perceived drug use as an indicator of poor adherence to antiretroviral therapy (Escaffre 2000). However, predictions by medical providers of which patients are likely to be adherent to HAART are often inaccurate (Bangsberg 2001; Escaffre 2000; Gross 2002; L. G. Miller 2002; Paterson 2000). While some studies have linked active drug and/or alcohol use with poor adherence (Carrieri 2003; Chesney 2000; Haubrich 1999; Lucas 2001), others have not found significant differences in adherence between drug users and former or non-drug users (Broers 1994; Gebo 2001; Roca 1999). The frequency of drug and/or alcohol use and the substance(s) being used vary, making generalizations about the impact of drug and/or alcohol use on adherence difficult.

For patients who are seeking treatment for drug and/or alcohol problems, combining primary care with addiction treatment may increase adherence to antiretroviral therapy (Lucas 2001; O'Connor 1992). However, treatment for drug and/or alcohol problems should not be a prerequisite for medical care for HIV and HCV. Barriers to adherence should be identified and addressed by several interventions, including screening for, and (when indicated) treating depression. Patients should receive education and counseling from HIV and HCV treatment education programs as well as their clinicians. Antiretroviral regimens should be selected carefully to reflect patient concerns regarding side effects, dosing frequency, pill burden and dietary restrictions (Murphy 2003; Proctor 1999; Starace 2002; Tucker 2003; Turner 2003). Interventions to support adherence, such as aggressive monitoring and management of side effects, ongoing counseling and provision of reminder devices and pill boxes should be incorporated into individually tailored adherence strategies (Haynes 2002; Stone 2001; Tuldra 2002).

Education About Addiction

Education on drug and/or alcohol addiction and treatment must be available to medical providers, some of whom have cited difficulties in providing care to people with drug and/or alcohol problems. A survey of 144 physicians reported that they experienced a lower satisfaction rate in caring for patients with drug and/or alcohol problems than those with other illnesses. Greater satisfaction in caring for patients with drug and/or alcohol problems was associated with a positive attitude towards treatment of addictions (adjusted OR 4.60, 95% CI, 1.59–13.29), physician confidence in assessment and intervention (adjusted OR, 2.49; 95% CI, 1.09–5.69) and perceived responsibility for addressing problems with substance use (adjusted OR 5.59, 95% CI, 2.07–15.12) (Saitz 2002).

These low satisfaction rates may reflect a lack of training on the identification and treatment of addiction. An astonishing 41% (28/66) of accredited medical schools surveyed in 1996 did not include curricula on addiction in lecture or discussion hours (N. S. Miller 2001). A national survey of 769 faculty members who teach residents about drug and alcohol problems reported that less than 10% of the instructors had actually done clinical work in alcohol or drug treatment programs, and only 19% were certified in addiction treatment (M. F. Fleming 1999).

Providing training on assessment of, and interventions for addiction increases physician confidence and comfort with providing care for people with drug and alcohol problems. Karam-Hage and colleagues surveyed attitudes and beliefs about addiction among 52 general psychiatry residents before and after a one-day educational conference on addiction. After the conference, participants were more likely to believe they could motivate patients to seek treatment for drug and/or alcohol problems, and had an increased interest in more training on addiction (Karam-Hage 2001). The University of Massachusetts Medical School has provided an intensive one or two-day interclerkship on substance abuse for third-year medical students and performed an evaluation on its impact on their knowledge and attitudes concerning substance abuse. After the interclerkship, participants had significant improvements in their ability to assess for drug and/or alcohol problems ($P=0.005$) and to provide appropriate intervention ($P<0.05$) (Matthews 2002). Curricula on assessment and interventions for addiction must be included in medical education, and CME programs.

Harm Reduction as Part of Medical Care

Harm reduction—a set of practical strategies that reduce negative consequences of drug use by addressing the conditions of drug use along with drug use itself—must be incorporated into the care and treatment of coinfected injection drug users. Instruction on safe injection practices and referral to syringe exchange programs or prescription of syringes will reduce the risk of HCV reinfection, bacterial infections and infection with other bloodborne pathogens. Resources are available to physicians to support integration of harm reduction into medical care; there are more than 200 syringe exchange programs in the United States (Edlin 2002). Prescription of syringes is illegal in only three jurisdictions (Burris 2002). A survey of 39 infectious disease and addiction medicine physicians in Rhode Island reported that 95% of respondents felt that there was a legitimate medical reason for injection drug users to obtain sterile syringes (Rich 2001).

Other interventions include referral to methadone maintenance programs or prescribing buprenorphine (a semi-synthetic opiate approved by the FDA in 2002 for maintenance and

detoxification treatment of opiate addiction). Although methadone is a safe and effective treatment for opioid addiction, its availability is limited; in the United States; only 20% of the estimated 810,000 heroin addicts receive methadone maintenance treatment (Office of National Drug Control Policy 2000). Buprenorphine is subject to fewer restrictions—doctors may apply for a waiver to prescribe or dispense it— and it has been associated with increased adherence to antiretroviral therapy (Moatti 2000). High-dose burpenorphine for treatment of opiate addiction has been available by prescription in France since 1996. A prospective study of retention in care among recipients of prescription high-dose buprenorphine found that 56.9% (508/909) were still with the same physician two years later. Their self-reported heroin use had decreased significantly ($P<0.001$), while their social situations (housing and work) improved significantly ($P<0.001$). The rates of seroconversion for HCV and HIV were low (4.1% and 0.8%, respectively) (Fhima 2001).

Recommendations

Provide full access to hepatitis C care and treatment for all HIV-positive persons in need.

Current treatments for HCV can cost as much as $40,000 per year. Cash-strapped State AIDS Drug Assistance Programs (ADAPs) are unable to offer HCV treatment; few have the resources available to provide pegylated interferon and ribavirin. ADAPs 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.

Include HIV/HCV coinfected individuals in early-phase HCV treatment trials.

Hepatitis C treatment with pegylated interferon plus ribavirin is less effective in coinfected persons (Chung 2004; Pérez-Olmeda 2003b; Perronne 2002, Perrone 2004; Torriani 2004). Because HCV is more aggressive in HIV-positive individuals, the need for new, more effective treatments is particularly urgent. Research on the safety and efficacy of HCV treatment in coinfected individuals has lagged; usually, coinfected individuals and clinicians must wait for several years before these data are available to them. This is unacceptable. Coinfected individuals must be offered the opportunity to participate in clinical trials of new agents as soon as it is safe to do so. A good benchmark here would be to ensure enrollment of coinfected individuals as soon as a safe and active dose is defined. Trial sponsors could stratify such studies by HIV status.

Explore Strategies to Optimize HCV Treatment for HIV/HCV-Coinfected Persons.

In the absence of new drugs, research on strategies for optimizing current HCV treatment for HIV/HCV-coinfected persons is needed. Sustained virological response rates from three large, randomized HCV treatment trials in HIV/HCV-coinfected persons have been disappointing, especially for people with genotype 1. Extending treatment from 48 weeks to 72 weeks may increase sustained virological response rates among this population. Although induction therapy with high-dose interferon has not been a successful intervention for people with HCV monoinfection, it may improve treatment outcomes for coinfected people. NIH should sponsor this research.

Side effects of HCV therapy may have severe consequences for coinfected people. For example, anemia, weight loss and depression are common side effects of HCV therapy. These are significant concerns for HIV-positive people, as all three conditions, when untreated, have been associated with more rapid HIV disease progression and poorer survival (Diallo 2003; Fairnpour 2003; Lundgren 2003; Mocroft 1999b; Moore 1998; Semba 2002; Sullivan 2002; Tate 2003; Wheeler 1998; Wheeler 1999; Williams 1999).

Ribavirin and both formulations of interferon may potentiate side effects and toxicities from antiretroviral agents (Anderson 2004; Berenguer 2003a; Braü 2004; Fleischer 2003; Lafeuillade 2001; Moreno 2004; Pérez-Olmeda 2003b; Perronne 2002; Pol 2003b; Salmon-Céron 2001; D. M. Smith 2002). Continued research on side effect management strategies for coinfected people during HCV treatment is crucial. Drug-drug interactions between agents used for HCV and HIV therapies need further study. Manufacturers of HCV and HIV therapies should offer their sponsorship for such research.

Interventions such as pre-emptive treatment for anemia and depression prior to, or upon initiation of HCV therapy may increase tolerability and adherence and thus, the likelihood of achieving SVR. These and other strategies for managing side effects and improving HCV treatment outcomes merit prospective, randomized trials. Manufacturers of HIV and HCV therapies, growth factors and anti-depressants should contribute their support towards this research.

Increase research of HCV treatment safety and efficacy in understudied coinfected populations.

HCV treatment trials in coinfected individuals have excluded people with medical and psychiatric co-morbidities; active drug users have been virtually excluded as well. Since HIV/HCV-coinfection is prevalent among injection drug users and individuals with severe mental illness, HCV treatment trials must be designed to include them. This will ensure that results will be applicable to these high-prevalence populations.

Coinfected individuals with compensated cirrhosis have an urgent need for treatment, yet little is known about the safety and efficacy of pegylated interferon–based regimens in this group. More research is needed.

The NIH must support research on the safety and efficacy of HCV treatment in these understudied coinfected populations.

Develop a treatment protocol for acute HCV infection in HIV-positive people.

As in HCV monoinfection, the optimum regimen and duration of treatment for acute hepatitis C infection are unknown. The NIH should support research on treatment of acute HCV infection in HIV-positive people.

Strengthen linkages between substance abuse treatment programs, methadone maintenance programs, medical and mental health providers, and HIV/HCV prevention and service programs.

Between 1994–2000, 7,955 current and former injection drug users who had already developed AIDS were tested for HIV (CDC 2002c). Since HCV is highly prevalent among IDUs, it is safe to assume that a majority of these individuals are HCV-coinfected. HAART has significantly decreased overall and liver-related mortality (Qurishi 2003), but when people present with advanced HIV disease and/or advanced liver disease, they may be unable to benefit fully from treatment for one or both infections (Wood 2003). Efforts to reach underserved and at-risk populations and provide them with medical care must increase.

Public and private systems of care must address multiple needs: mental health, addiction, medical care and treatment. Linkages between prevention programs for HIV and HCV and medical care delivery systems must be strengthened.

Increase capacity to provide individualized medical care and treatment to coinfected active drug users.

Harm reduction must be incorporated into the medical care of coinfected injection drug users. Interventions must range from education on safer drug use to supporting abstinence and recovery.

Adequate education on assessment of and treatment for drug and alcohol addiction is an important component of providing care to active and recovering drug and/or alcohol users. Cross-disciplinary collaboration between injection drug users, medical providers, experts in harm reduction and substance abuse treatment are necessary to develop best practices for medical care for coinfected injection drug users. The National Institutes of Health and its National Institute on Drug Abuse (NIDA) should support the development of best practices for treatment of coinfected injection drug users.

Support access to and research on organ transplantation for HIV-positive individuals

Although HAART has significantly increased the survival of HIV-positive individuals, the risk for end-stage organ disease in this population remains significant. In the HAART era, HIV-positive individuals may have post-transplantation outcomes equivalent to HIV-negative individuals (Gow 2001; Kuo 2001; Neff 2003c, Prachalias 2001; Ragni 1999; Ragni 2003a; Ragni 2003b; Roland 2002; Roland 2003; Roland 2004; Rufi 2004).

Although The United Network for Organ Sharing (UNOS) does not consider HIV infection to be a contraindication for organ transplantation, its policy on transplantation has not been updated for more than a decade. Consequently, the UNOS policy does not reflect virological, immunological and survival benefits from the use of highly active antiretroviral therapy. A revised policy may help dispel the unwillingness to perform transplantation in HIV-positive candidates at individual transplant centers, where the decision to perform transplantation in HIV-positive candidates is made.

Despite the emerging reports of favorable outcomes in HIV-positive individuals, insurers have sometimes denied reimbursement for transplants when HIV is involved, deeming it “experimental.” Expanding an indication to include people with HIV does not transform an established procedure into an “experiment.” Transplantation must be reimbursable for HIV-positive individuals.

The National Institutes of Health has funded a prospective, multi-center cohort study evaluating the safety and efficacy of solid organ (kidney and liver) transplantation in people with HIV. An evaluation of the effect of MELD on the survival of HIV-positive transplant candidates and organ recipients will be included.

This and other prospective studies of transplantation in HIV-positive individuals will provide vitally important information about the specific risks for those undergoing transplantation, as well as help to identify the optimal clinical management strategies for improved and extended survival of HIV-positive organ recipients. This important research—and transplantation in HIV-positive candidates outside of research settings— will provide crucial data that may be used to broaden indications and secure reimbursement for transplantation in HIV-positive candidates.

List of Terms Used in This Chapter

Absolute CD4 cell count: the number of CD4 lymphocytes in one cubic millimeter (mm^3) of blood.

Anitemetic: a drug used to control nausea and vomiting.

Buprenorphine: a semi-synthetic opiate. Buprenorphine was approved by the FDA in 2002 for maintenance and detoxification treatment of opiate addiction.

CD4 cell percentage: the percentage of total lymphocytes made up by CD4 CELLS. Hemolysis: destruction of red blood cells. When the membrane of a red blood cell is ruptured, hemoglobin is released from the cell.

Hemoglobinuria: an abnormal condition marked by the presence of hemoglobin in urine.

Hyperamylasemia: abnormally high levels of amalyse in the blood or urine. Amalyse is a digestive enzyme produced by the pancreas and salivary glands.

Myleosuppression: a decrease in the ability of the bone marrow cells to produce blood cells, including red blood cells, white blood cells and platelets.

Negative predictive value (NPV): The accuracy of predictions that the target outcome is not present. In this case, a sustained virological response to hepatitis C treatment was not present, based on virological response to hepatitis C treatment at a specific timepoint during treatment (such as week 4 or week 12). For example, an NPV of 99% means that a 99/100 people without a virological response to hepatitis C treatment at week 12 did not achieve a sustained virological response.

Optic neuropathy: damage to the optic nerve, which may result in impairment or loss of vision.

Pancreatitis: inflammation of the pancreas. Pancreatitis is a potentially life-threatening condition. Symptoms include: severe abdominal pain, nausea, vomiting, constipation, and slow pulse. The onset of pancreatitis can be predicted by rises in blood levels of the pancreatic enzyme amylase.

Peripheral neuropathy: nerve damage characterized by sensory loss, pain, muscle weakness and wasting of muscle in the hands or legs and feet. It may start with burning or tingling sensations or numbness in the toes and fingers.

Phosphorylation: the addition of a phosphate group to an organic molecule.

Positive predictive value (PPV): the proportion of all people who were identified by a measurement or screening test as apparently having a target outcome who actually do have the target outcome. In this case, PPV refers to the proportion of people who have a virological response to hepatitis C treatment at a specific timepoint during treatment (such as week 4 or week 12) who will actually achieve a sustained virological response. For example, a PPV of 50% means that 50/100 people who had a virological response to hepatitis C treatment at week 12 achieved a sustained virological response.

Sepsis: an infection in the bloodstream or tissues

Symptomatic Hyperlactatemia: mild to serious elevations in serum lactate levels. accompanied by symptoms including fatigue, anorexia, nausea, abdominal pain, weight loss.

Treatment naïve: a person who has never received any treatment for a specific condition. Upregulation: an increase in the rate at which something occurs.