AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 22, Number 4, 2006, pp. 315–320

Efficacy and Safety of Pegylated Interferon-α2b Plus Ribavirin for the Treatment of Chronic Hepatitis C in HIV-Infected Patients

MIGUEL SANTIN,[1] EVELYN SHAW,[1] M. JOSE GARCIA,[2] ANTONIO DELEJIDO,[3] EDUARDO RODRIGUEZ DE CASTRO,[4] ROSA ROTA,[5] JORDI ALTÉS,[6] FRANCISCO BAGUENA,[7] SILVIA VALERO,[8] MONTSERRAT SALA,[9] AURORA CASANOVA,[10] and the HCV/HIV-01 STUDY TEAM

ABSTRACT

Low response rates and concerns about safety have limited the implementation of treatment for chronic hepatitis C (CHC) in patients with HIV infection. The efficacy and safety of pegylated interferon (peg-IFN) plus ribavirin in HIV-infected patients with CHC were evaluated in a prospective, open-label, multicenter study. Sixty patients with persistently high transaminases, positive HCV-RNA, CD4 count ≥300 cells/μl, and HIV-RNA <10,000 copies/ml were included. Patients were given peg-IFN 80–150 μg/week plus ribavirin 800–1200 mg/day. Treatment was scheduled for 24 weeks for genotypes 2/3 and 48 weeks for genotypes 1/4. In an intent-to-treat analysis, 16 (26.7%) patients achieved a sustained virological response (SVR). Twenty patients (33.3%) discontinued treatment prematurely, but only in 10 (16.6%) was discontinuation due to adverse events. Negative predictive values for SVR on the basis of HCV-RNA decline between baseline and week 4 were 100% for 1- and 2-$\log_{10}$ fall, and positive predictive values were 40% and 58.3% for 1- and 2-$\log_{10}$ fall, respectively. CD4 fell by a median of 216 cells during treatment, but no HIV-associated complications occurred. In conclusion, treatment with peg-IFN alfa-2b plus ribavirin is safe and clears RNA-HCV in about one-quarter of HIV-infected patients with CHC. Efforts should be focused on optimizing management of side effects and counseling to improve adherence and to keep patients on treatment. Assessment of HCV-RNA at week 4 may help guide early therapeutic decision making.

INTRODUCTION

As a result of the improved prognosis of HIV disease in the last decade, hepatitis C virus (HCV)-associated liver disease has emerged as a leading cause of morbidity and mortality in HIV/HCV coinfected patients.[1–3] To avoid progression to end-stages of liver disease, treatment with pegylated interferon (peg-IFN) plus ribavirin is currently recommended for chronic hepatitis C (CHC) in patients with preserved immune status and a good control of HIV replication.[4,5] However, low virological response rates, the uncertainty surrounding long-term efficacy, and concern regarding the safety of combined therapy frequently dissuade clinicians from treating these patients.[4] In addition to the well-recognized adverse events, the increased risk of severe lactic acidosis, pancreatitis, and hepatic decompensation in the course of treatment with concomitant antiretroviral therapy is of special concern.[6–8] The real extent of this problem is unknown, but certain risk factors have been identified, such as treatment with didanosine.[8,9]

In mid-2001, the encouraging results obtained in non-HIV

[1]Infectious Diseases Service, IDIBELL, Hospital Universitari de Bellvitge, Barcelona, Spain.
[2]Gastroenterology Service, Hospital de Can Misses, Ibiza, Spain.
[3]Internal Medicine Service, Hospital de St Pau i Sta Tecla, Tarragona, Spain.
[4]Internal Medicine Service, Hospital Verge del Toro, Menorca, Spain.
[5]Gastroenterology Service, Hospital de Viladecans, Barcelona, Spain.
[6]Internal Medicine Service, Hospital de l'Alt Penedès, Vilafranca, Spain.
[7]Internal Medicine Service, Hospital d' Igualada, Barcelona, Spain.
[8]Internal Medicine Service, Hospital Sant Jaume de Calella, Barcelona, Spain.
[9]Internal Medicine Service, Hospital Parc Taulí, Sabadell, Spain.
[10]Microbiology Service, IDIBELL, Hospital Universitari de Bellvitge, Barcelona, Spain.

patients[10,11] prompted us to implement treatment of CHC in HIV-coinfected patients with a combination of peg-INF and ribavirin in our hospital and associated centers. Since at that time there was little experience with the combination in this population, an open prospective study was started to evaluate its efficacy and safety. Here we report our experience of treatment with peg-INF plus ribavirin for CHC in HIV-coinfected patients. We also evaluated the usefulness of RNA-HCV levels at week 4 of treatment as a predictor of sustained virological response (SVR) in a subset of patients.

MATERIALS AND METHODS

Study design

A prospective, open-label, multicenter study was conducted in 10 hospitals in Spain, from November 2001 to October 2002. The study was approved by the institutional review board at each center and informed consent was obtained for each patient recruited. All patients received the combination of pegylated IFN-α2b (Pegintron; Shering-Plough, Kenilworth, NJ) 80–150 μg (less than 60 kg, 80 μg; between 61 and 75 kg, 100 μg; between 76 and 85 kg, 120 μg, more than 85 kg, 150 μg), once a week subcutaneously, and ribavirin (Rebetol; Shering-Plough, Kenilworth, NJ) 800–1200 mg (less than 65 kg, 800 mg/day; between 66 and 85, 1000 mg/day, and more than 85 kg, 1200 mg/day) divided in two daily doses administered orally. Treatment was scheduled for an initial period of 24 weeks for all patients. According to the guidelines established by the Advisory Council for Treatment of Viral Hepatitis (Health Department of the Government of Catalonia),[12] treatment was discontinued at week 24 in patients without virological response (see below) and those with virological response harboring genotypes 2 and 3. In patients with genotypes 1 and 4 and virological response, treatment was extended to 48 weeks.

End-points

The primary end-point of the study was the SVR, defined as undetectable serum HCV-RNA 24 weeks after the end of treatment. The secondary end-point was early virological response (EVR), defined as a 1- or 2-log drop or undetectable HCV-RNA at week 4 of treatment.

Patients

Adult patients between 18 and 60 years were eligible if they had confirmed HIV infection, persistently elevated transaminase levels (on at least two occasions, 3 months apart), positive HCV antibodies, and detectable serum HCV RNA. Liver biopsy was not mandatory. As for HIV infection, patients were required to have $\geq$300 cells/μl and HIV RNA levels below 10,000 copies/ml (b-DNA). Exclusion criteria included active coinfection with hepatitis B virus, other liver diseases, decompensated cirrhosis, concomitant treatment with zidovudine, active drug abuse within the previous 12 months, alcohol intake, history of severe psychiatric illness, seizures, autoimmune disease, previous therapy with interferon, white blood cell count $<1500/mm^3$, platelet count $<85{,}000/mm^3$, and hemoglobin $<$12 g/dl for women and $<$13 g/dl for men. Patients with serum lactate more than four times above the upper limit, or twice the normal limit if receiving concomitant treatment with didanosine, were also excluded.

Patients' evaluation

Patients were evaluated as outpatients at weeks 2, 4, 12, and every 3 months thereafter. Laboratory tests were performed in each of the participating centers except for HCV RNA and genotyping, which were centralized in the Microbiology Department of the Hospital Universitari de Bellvitge. Serum HCV was assessed by the qualitative test (detection limit 50 IU/ml; Cobas Amplicor v2.0 kit, Roche Diagnostics Systems Inc.). Serum HCV RNA quantitation was carried out with the Cobas Amplicor HCV Monitor test v2.0 (Roche Molecular Systems, Branchburg, NJ) with a detection limit of 600 IU/ml. HCV genotyping was determined from the RNA extracted for quantitation using a test based on a restriction fragment length polymorphism (RFLP).[13] Briefly, HCV RNA was amplified by a nested RT-PCR on the 5′ UTR region of the HCV genome to obtain a 240-bp amplicon that was cleaved using three restriction endonucleases (*Mva*I, *Bsh*1236I, and *Mbo*I). The fragment pattern was analyzed by electrophoresis on agarose gels stained with ethidium bromide.

Safety was assessed by recording clinical adverse events and laboratory abnormalities. Severity of adverse events was graded as mild, moderate, severe, or life-threatening. Adverse events were evaluated for duration, relationship to the study medication, and action taken to relieve them. Stepwise reductions in the peg-IFN and ribavirin, according to predefined thresholds, were allowed for the management of adverse events. No growth factors (such as erythropoietin or granulocyte colony-stimulating factor) were used to manage hematologic toxicity.

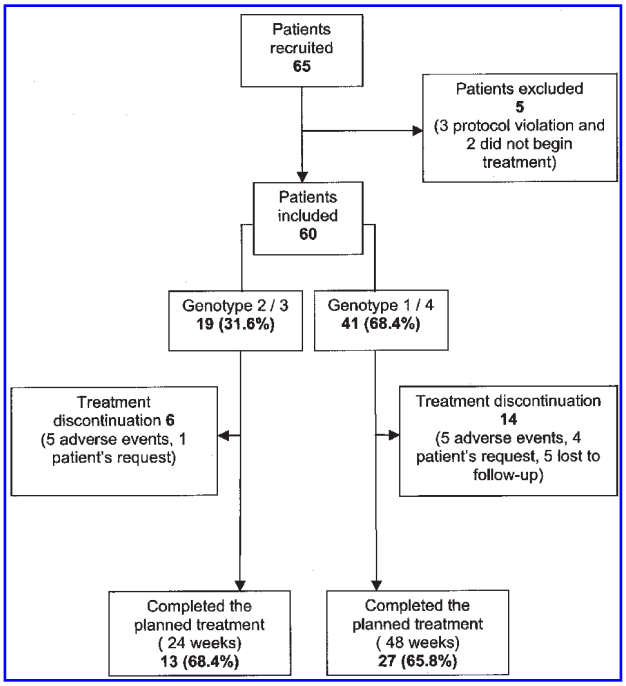

FIG. 1. Study profile.

Table 1. Baseline Characteristics of the 60 Patients

Characteristics	
Age, years mean (SD)	38.1 (5.3)
Sex, *n* (% male)	48 (80)
Weight, kg mean (SD)	71.7 (1.4)
Mode of infection, n (%)	
Intravenous drug use	50 (83.3)
Sexual	8 (13.4)
Others	2 (3.4)
Estimated duration of HCV infection, *n* (%)	
5–10 years	28 (46.7)
>10 years	29 (48.3)
Unknown	3 (5)
ALT levels, IU/liter, mean (SD)	128.5 (66.2)
AST levels, IU/liter, mean (SD)	101.6 (69.9)
HCV RNA $\log_{10}$, IU/liter	
Mean (SD)	6.06 (0.63)
Patients with >800,000, *n* (%)	39 (65)
Genotype, *n* (%)	
1	32 (53.4)
2	2 (3.3)
3	17 (28.3)
4	9 (15)
CD4 cell count, cells/mm^3, mean (SD)	645 (350.5)
HIV RNA $\log_{10}$, copies/ml, mean (SD)	2.17 (0.43)
Antiretroviral therapy, *n* (%)	
2 NRTIs + 1 NNRTI	36 (60)
2 NRTIs + 1 IP[a]	10 (16.7)
3 NRTIs	6 (10)
Others	2 (3.4)

[a]One patient received d4T, ddI, and a protease inhibitor.

Statistical analysis

With our understanding of the combined therapy with peg-IFN and ribavirin for CHC at the time of the study design, and assuming a poorer response in the HIV-coinfected population, we expected an SVR rate of 30%. It was estimated that a minimum of 56 patients (including 20% nonevaluable patients) were needed to give results for the primary end-point (SVR) within ±15% of the confidence interval, with a confidence level of 95% and a power of 80%. However, in case the drop-out rate was higher than expected, recruitment of patients after reaching the minimum sample size was allowed until the close of the inclusion period. Efficacy and safety analyses were based on the patients who received at least one dose of the study medication. Response rates were determined on an intention-to-treat basis. Patients lost to follow-up during the study period or with missing HCV RNA determinations were treated as failures. Additionally, an analysis based on the patients who completed the scheduled treatment was also performed (on-treatment analysis). The relation of baseline characteristics and SVR was assessed by univariate and stepwise forward logistic-regression analysis. Negative and positive predictive values (NPV and PPV) were calculated by 2×2 tables. Statistical analyses were performed using the SPSS 10.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Baseline characteristics

Sixty-five patients were recruited, of whom 5 (7.7%) were excluded (Fig. 1). The remaining 60 (92.3%) patients who took at least one dose of medication were included in the analysis. Most patients were men (80%), had acquired HIV infection by an intravenous route (83.3%), and were receiving effective antiretroviral therapy (90%). As for characteristics of HCV infection, the only relevant finding was a lower HCV RNA in the nine patients harboring genotype 4 (mean 5.23 ± 0.81 $\log_{10}$, median 5.4 $\log_{10}$) than in those with genotypes 1 and 3 (mean 6.24 ± 0.46 log10, median 6.3; $p = 0.005$). The main characteristics of patients at baseline are summarized in Table 1.

Efficacy

Twenty patients (33.3%; 95% CI 21.4–45.3%) had undetectable plasma HCV RNA at the end of treatment (EOT). At 6 months after stopping treatment, 16 patients (26.7%; 95% CI 15.5–37.9%) continued with undetectable HCV RNA levels and were considered as having SVR. Virological response rates according to genotype are shown in Table 2. Overall, out of 44 patients who failed to achieve SVR, 20 (45.5%) did not respond at the end of treatment, 20 (45.5%) discontinued treatment prematurely, and 4 (9.1%) initially responded but relapsed shortly after stopping treatment. Premature treatment discontinuation

Table 2. Virological Response at the End of Treatment and Follow-up

	On treatment		*Intent-to-treat*	
Genotype	*End of treatment response* n/N *(%)*	*Sustained response* n/N *(%)*	*End of treatment response* n/N *(%)*	*Sustained response* n/N *(%)*
1	7/23 (30.4)	6/23 (26)	7/32 (21.8)	6/32 (18.7)
2	0/2 (—)	0/2 (—)	0/2 (—)	0/2 (—)
3	10/11 (90.9)	8/11 (72.7)	10/17 (58.8)	8/17 (45.1)
4	3/4 (75)	2/4 (50)	3/9 (33.3)	2/9 (22.2)
Overall	20/40 (50)	16/40 (40)	20/60 (33.3)	16/60 (26.7)

in 10 of 20 patients (50%) was at the patient's request, or due to losses to follow-up. Patients infected with genotype 3 and with low plasma HCV RNA at baseline had a higher SVR rate. Univariate and multivariate analyses of predictors of SVR are shown in Table 3.

Predictive value of virological response at week 4

HCV-RNA level was assessed at week 4 in 48 patients. Thirty-five (73%) and 25 (52%) patients had at least 1-$\log_{10}$ and 2-$\log_{10}$ reduction from baseline, respectively. There were no significant differences between genotypes in the proportion of patients who achieved 1 $\log_{10}$ reduction: 13 of 15 patients (86.6%) with genotype 2/3 and 22 of 33 (66.7%) with genotype 1/4 had at least 1-$\log_{10}$ reduction from baseline ($p = 0.18$). But, there were differences when 2-$\log_{10}$ reduction was considered: 13 of 15 patients (87%) with genotypes 2/3 had at least 2-$\log_{10}$ reduction, as compared with 12 of 33 (36%) with genotypes 1/4 ($p = 0.002$). None of the 13 patients with less than 1 $\log_{10}$ HCV-RNA reduction and 14 of the 35 (40%) with at least 1-$\log_{10}$ reduction achieved SVR ($p = 0.01$). When a cut-off of a 2-$\log_{10}$ fall was considered, none of the 24 below this figure achieved SVR, as compared to 14 of 24 (58.3%) above it ($p < 0.001$). NPVs were 100% (95% CI 72–100%) for 1 $\log_{10}$ reduction and 100% (95% CI 83–100% for 2 $\log_{10}$ reduction, and PPVs were 40% (95% CI 24–57%) and 58% (95% CI 37–72%) for 1 and 2 $\log_{10}$ reduction, respectively.

Safety

During treatment 57 patients (95%) presented adverse events, which were serious (grade III/IV) in 10 (16.7%) (Table 4). Overall, dose reduction of medication due to adverse events was necessary in 7 patients (11.7%), and permanent discontinuation of one or two of the drugs in 10 (16.7%). Flu-like syndrome was the most frequent adverse event observed (76.6% of cases), and led to treatment discontinuation in two cases (3.2%). In addition to these two cases, in four of five patients who asked to leave the study, flu-like symptoms (though considered mild by the investigators) significantly contributed to their decision. As for hematological alterations, only neutropenia reached grade III–IV severity in three cases, and was responsible for treatment discontinuation in two. Six patients (10%) developed anemia during treatment: none was severe and treatment discontinuation

Table 3. Predictors Factors of Sustained Virological Response (Univariate and Multivariate Analyses)

Variable	N	*Responders* N *(%)*	*Crude RR (95% CI)*	p	*Adjusted RR (95% CI)*	p
Age (years)						
<40	35	9 (25.7)	1			
≥40	25	7 (28)	1.1 (0.4–3.6)	0.84		
Sex						
Female	12	1 (8.3)	1			
Male	48	15 (31.3)	5.0 (0.6–42.3)	0.14		
Weight[a]						
≥70	27	7 (25.9)	1			
<70	30	9 (30)	1.2 (0.4–3.9)	0.73		
HIV/HCV acquisition						
Others	10	1 (10)	1			
Intravenous drug use	50	15 (30)	3.9 (0.4–33)	0.22		
AIDS						
Yes	15	2 (13.3)	1			
No	45	14 (31.1)	2.9 (0.6–14.8)	0.19		
CD4 cell count (cells/mm^3)[b]						
≥500	36	9 (25)	1			
<500	23	7 (30.4)	1.3 (0.4–4.2)	0.65		
Antiretroviral therapy						
Yes	54	14 (25.9)	1			
No	6	2 (33.39)	1.4 (0.2–8.7)	0.70		
ALT (IU/ml)	60	16 (26.7)	1.0 (0.9–1.0)	0.26		
Genotype 3						
No	17	8 (47.1)	1		1	
Yes	43	8 (18.6)	3.9 (1.1–13.2)	0.03	5.0 (1.3–19.9)	0.02
Plasma HCV RNA (UI/ml)						
≥800,000	38	6 (15.8)	1		1	
<800,000	22	10 (45.5)	4.4 (1.3–14.9)	0.02	5.6 (1.5–21.2)	0.01
Treatment modification (dose reduction)						
No	53	14 (26.4)	1			
Yes	7	2 (28.6)	1.1 (0.2–6.4)	0.90		

[a]Data available for 57 patients.
[b]Data available for 59 patients.

TABLE 4. ADVERSE EVENTS DURING TREATMENT

Adverse event	N *(%)*	*Grade III or IV events*	*Cause of treatment discontinuation*
Flu-like symptoms	46 (76.6)	3 (5)	2 (3.3)
Weight loss	22 (36.6)	—	
Psychiatric disorders	20 (30)	3 (5)	4 (6.7)
Psychosis	4	1	3
Depression	8	1	1
Irritability/insomnia	9	—	—
Hematological alterations	22 (36.6)	3 (5)	2 (3.3)
Anemia	6	—	
Neutropenia	17	3	2
Thrombocytopenia	13	—	
Respiratory symptoms	4 (6.6)	1 (1.6)	1 (1.7)
Dyspnea	4	1	1
Dermatological alterations	14 (23.3)	—	1 (1.7)
Injection-site reaction	13		
Generalized rash	1		1

was not necessary in any case. Hemoglobin levels decreased progressively from baseline to week 12: median 15.5 g/liter at baseline, 13.3 g/liter at week 4, and 13.2 g/liter at week 12. No deaths, lactic acidosis, pancreatitis, or new or unexpected adverse events were seen. CD4 cell counts decreased by a median of 216 cells from the baseline to the end of treatment (data assessed in 34 of 40 patients who completed treatment). No increases in HIV-RNA were observed in any patient during treatment.

DISCUSSION

Our results show that the combination of peg-IFN alfa-2b plus ribavirin clears HCV-RNA in about 25% of HIV-infected patients with CHC. This response rate is lower than those recently reported in coinfected subjects[14,15] and in HCV single-infected populations.[10,11] The APRICOT study,[14] a comparative clinical trial of peg-IFN alfa-2a plus ribavirin with combined standard therapy and peg-IFN alone in coinfected patients, reported an SVR rate of 40% in the peg-IFN alfa-2a plus ribavirin arm. Similar results were found in another smaller study comparing the combination of peg-IFN alfa-2b plus ribavirin with standard therapy.[15] In contrast, data from the RIBAVIC study[9] with peg-IFN alfa-2b plus ribavirin obtained an SVR rate of 27%, a figure closer to ours and to those reported previously in an open-label study.[7] In addition to differences in patients' baseline characteristics, methodology, therapeutic regimens, and study settings, premature discontinuation rates make a significant contribution to the huge discrepancies in efficacy rates. Thirty-nine percent of patients treated with peg-IFN and ribavirin discontinued treatment in the RIBAVIC study, as compared to 25% in the APRICOT study. In our series premature treatment discontinuation was recorded in 33% of cases. Notably, half of the discontinuations were at the patient's request or due to losses to follow-up, a circumstance that probably reflects a lack of expertise on the part of some treating teams in management and counseling aimed at improving adherence and keeping patients on treatment.

As regards safety, the combination of peg-IFN alfa-2b plus ribavirin was relatively well tolerated. However, psychiatric disorders are of special concern, because of their potential severity and the high rate of treatment discontinuation. No deaths, life-threatening complications such as lactic acidosis and pancreatitis,[6–8,16] or new or unexpected adverse events were seen. In addition, a high rate of liver decompensation in the course of treatment was reported in coinfected patients with histologically proven cirrhosis.[8] Concomitant treatment with didanosine, increased bilirubin levels, decreased hemoglobin, increased alkaline phosphatase, or decreased platelets was identified as the major risk-associated factor.[8] In our study, in which no patients presented evidence of hepatic insufficiency before initiation of treatment and only one received didanosine, none of these major complications was seen.

As in previous reports, we found no opportunistic infections during treatment, and the HIV viral load remained under control. However, given the high median CD4 cell count of the patients included, fewer than 10% fell below 200 cells despite a pronounced decline during treatment. So HIV-associated complications may appear if treatment is given to patients with lower CD4 cell counts.

Two points of our study merit further comment: the duration of treatment for genotypes 2 and 3 and the predictive value of RNA-HCV at week 4 of treatment. A 24-week regimen for genotypes 2 and 3 was adopted in the present study, following the guidelines established by the local health authorities when the study was designed. What our results indicate is that 24 weeks of therapy is sufficient for some coinfected patients with genotype 2 or 3. However, as observational data[17] show, relapses are unexpectely high among patients treated for 24 weeks. So, until prospective clinical trials are able to identify favorable response factors that make it possible to shorten treatment for genotypes 2 or 3, a 48-week therapy regimen should be offered to all HIV-coinfected patients regardless of genotype.

As regards early virological response as a prognostic factor of SVR, our data show that patients who did not have a substantial reduction of RNA-HCV by week 4 of treatment did not

achieve long-term response. Although the confidence interval around this estimate is wide, these data strongly suggest that assessment of HCV-RNA level at week 4 of treatment may accurately identify patients with no chance of achieving SVR. Since slow responses were reported in some patients, a 1-log rather than 2-log reduction may be a more reliable cut-off to identify patients with no chance of responding. These results are in agreement with other recently published findings and should be confirmed in larger controlled clinical trials.[18] Meanwhile, treatment should be discontinued if a fall of at least 2-log is not achieved by week 12.[4]

In summary, in our experience, the combination of peg-IFN alfa-2b plus ribavirin clears HCV-RNA in about one-quarter of HIV-infected patients with CHC. This low SVR was mainly related to a high drop-out rate; however, premature discontinuation of treatment was due to serious adverse events in only 17% of cases. Efforts should be focused on optimizing management of side effects and counseling to improve adherence and keep patients on treatment. Assessment of HCV-RNA level at week 4 of treatment may help guide early therapeutic decisions, and merits further exploration in larger controlled clinical trials.

ACKNOWLEDGMENTS

This study was partially supported by a grant from Shering-Plough, Spain.

Members of the HIV/HCV-01 Study Team: Dra. M.J. Barberá, Dra. B. Rosón, Dr. D. Podzamczer, Dra. C. Baliellas, Hospital Universitari de Bellvitge; Dra. E. Dorca, Hospital General de Manresa; Dr. M. Guadarrama and Dr. J. Guardiola, Hospital de l'Alt Penedès.

REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, *et al*.: Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient study investigators. N Engl J Med 1998;338:853–860.
2. Soriano V, Garcia-Samaniego J, Valencia E, Rodriguez-Rosado R, Muñoz F, and Gonzalez-Lahoz J: Impact of chronic liver disease due to hepatitis viruses as cause of hospital admission and death in HIV-infected drug users. Eur J Epidemiol 1999;15:1–4.
3. Sulkowski M and Thomas D: Hepatitis C in the HIV-infected person. Ann Intern Med 2003;138:197–207.
4. Soriano V, Puoti M, Sulkowski Mark, *et al*.: Care of patients with hepatitis C and HIV co-infection. AIDS 2004;18:1–12.
5. Strader DB, Wright T, Thomas DL, and Seeff LB: Diagnosis, management and treatment of hepatitis C. Hepatology 2004;39:1147–1171.
6. Sauleda S, Juárez A, Esteban JI, *et al*.: Interferon and ribavirin combination therapy for chronic hepatitis C in human immunodeficiency virus-infected patients with congenital coagulation disorders. Hepatology 2001;34:1035–1040.
7. Pérez-Olmeda M, Núñez M, Romero M, *et al*.: Pegylated IFN-α2b plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. AIDS 2003;17:1023–1028.
8. Mauss S, Valenti W, DePamphilis, *et al*.: Risk factors for hepatic descompensation in patients with HIV/HCV coinfection and liver cirrhosis during interferon-based therapy. AIDS 2004;18:F21–F25.
9. Carrat F, Bani-Sadr F, Pol S, *et al*.: Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients. JAMA 2004;292:2839–2848.
10. Manns MP, McHutchinson JG, Gordon SC, Rutgi VK, Shiffman M, Reindollar R, *et al*.: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomised trial. Lancet 2001;358:958–965.
11. Fried MW, Shiffman ML, Reddy KR, *et al*.: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–982.
12. Consell Assessor for Treatment of Viral Hepatitis. Department of Health. Generalitat de Catalunya: http://www.gencat.net/sanitat/portal/cat/catfhv.htm.
13. Thiers V, Jaffredo F, Tuveri R, Chodan N, and Bréchot Ch: Development of a simple restriction fragment length polymosphism (RFLP) based assay for genotyping and comparative analysis with genotyping and serotyping tests. J Virolog Methods 1997;65:9–17.
14. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, *et al*.: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004;351:438–450.
15. Laguno M, Murillas J, Blanco JL, *et al*.: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS 2004;18:F27–F36.
16. Lafeuillade A, Hittinger G, and Chadapaud S: Increased mitochondrial toxicity with ribavirin in HIV / HCV coinfection. Lancet 2001;357:280–281.
17. Soriano V, Perez-Olmeda M, Rios P, Nuñez M, Garcia-Samaniego J, and Gonzalez-Lahoz J: Hepatitis C virus (HCV) relapses after anti-HCV therapy are more frequent in HIV-infected patients. AIDS Res Hum Retroviruses 2004;20:351–353.
18. Ballesteros AL, Franco S, Fuster D, *et al*.: Early HCV dynamics on peg-interferon and ribavirin in HIV/HCV co-infection: Indications for the investigation of new treatment approaches. AIDS 2004;18:59–66.

Address reprint requests to:
Miguel Santin
Infectious Diseases Service
IDIBELL
Hospital Universitari de Bellvitge
C/ Feixa Llarga s/n
08907 L'Hospitalet, Barcelona, Spain

E-mail: msantin@csub.scs.es