Interferon α for the Treatment of Chronic Hepatitis C in Patients Infected with Human Immunodeficiency Virus

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Liver disease secondary to hepatitis C virus (HCV) infection is a rising cause of morbidity and mortality among individuals who have been infected parenterally with human immunodeficiency virus (HIV) such as injection drug users, hemophiliacs, and transfused patients. We analyzed both the efficacy of interferon (IFN) α therapy in these patients and the predictors of response to this agent. A total of 119 patients with chronic hepatitis C (90 of whom were infected with HIV and 29 of whom were not) were included in a multicenter, prospective, open, nonrandomized observational study. IFN-α was given subcutaneously in a dosage of 5 million units three times a week during a 3-month period; those patients who responded received a dose of 3 million units given subcutaneously three times a week for an additional 9 months. One hundred seven patients completed the study; the level of aminotransferases returned to normal and sera became negative (complete response) for HCV RNA in 26 (32.5%) of 80 HIV-infected patients and 10 (37.0%) of 27 non-HIV-infected patients (P = .666) after completion of the treatment. Two variables were independently associated with a response in HIV-infected patients: a $CD4^+$ T lymphocyte count of $>500 \times 10^6$/L and a baseline HCV viremia level of $<10^7$ copies/mL. In the 12 months following treatment, relapses occurred in 30.8% of the HIV-infected patients and 12.5% of non-HIV-infected patients (P = .403).

Until recently, the life expectancies of patients infected with HIV have been compromised by several opportunistic infections that develop when the $CD4^+$ T lymphocyte count falls below a critical level [1]. As a result, the presence of other illnesses such as chronic liver disease represented a less serious problem because many of these patients had already died of their infections. However, the introduction in the late 1980s of antiretroviral drugs, especially zidovudine and didanosine, and the wide availability of primary prophylaxis for the most common opportunistic infections (e.g., *Pneumocystis carinii* pneumonia) have prolonged the asymptomatic period and survival among HIV-infected patients [2, 3].

A change in recent years in the spectrum of illnesses associated with HIV infection has meant that certain previously unimportant diseases are now relevant [4, 5]. Chronic viral liver disease, particularly chronic hepatitis C, is one of these conditions and is most frequently seen in countries where injection drug users (IDUs) constitute a significant proportion of the HIV-infected population; chronic hepatitis C is certainly a growing cause of morbidity and mortality in this group [5–7].

Treatment with interferon (IFN) α is recommended for non-HIV-infected patients with chronic hepatitis C [8]. However, there are no established guidelines for treatment of patients coinfected with HIV [8]. Preliminary results from a limited number of studies suggest that treatment with IFN-α is successful in more than one-third of patients [9–11]; this rate is similar to that observed for non-HIV-infected patients with chronic hepatitis C. At present the variables that can predict a complete response to therapy with IFN-α for chronic hepatitis C in HIV-infected patients are unknown.

The Hepatitis-HIV Spanish Study Group was established in 1992. The primary objective of the group was to define the efficacy and safety of IFN-α therapy for chronic hepatitis C in HIV-infected patients who were not severely immunocompromised. A second aim was to investigate whether predictors of response to therapy with IFN-α in this population could be defined.

Methods

In March 1992 a multicenter, prospective, open, nonrandomized study was started in Spain to assess the efficacy and safety of recombinant IFN-α2b (Intron-A, Schering-Plough, Bloomfield, NJ) for treating chronic hepatitis C in HIV-infected patients with $CD4^+$ T cell counts of $>200/\mu$L. Non-HIV-infected patients with chronic hepatitis C were enrolled at the same time as controls. The recruitment period ended in December 1993.

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Patients. A diagnosis of chronic hepatitis C was based on the following criteria: (1) an alanine aminotransferase (ALT) level that was twofold or more above the normal upper limit in at least two blood samples collected within an interval of >6 months; (2) the presence of antibodies to hepatitis C virus (HCV) proteins, as determined by a second-generation EIA and confirmed by a second-generation immunoblot assay (CHIRON RIBA HCV test, Ortho Diagnostic Systems, Raritan, NJ) that was considered positive when at least two bands were reactive; and (3) liver biopsy results compatible with chronic active hepatitis, with or without cirrhosis. Patients who were positive for hepatitis B surface antigen, reported an alcohol intake of >60 g/d, and/or had evidence of other conditions (e.g., autoimmune disease, metabolic disease, or use of drugs that could cause chronic hepatitis) were excluded from the study.

All patients underwent liver biopsy before IFN-α therapy was begun, but this procedure was not repeated after completion of the 12-month course of treatment. The Knodell scoring system, known as the histological activity index [12], was used to evaluate pretreatment liver biopsy specimens.

Patients were eligible for IFN-α therapy if they met the following criteria: a diagnosis of chronic hepatitis C (based on the criteria listed above); age, >18 years; voluntary participation; a $CD4^+$ T lymphocyte count of >200/μL in HIV-infected patients; a neutrophil count of >1,500/μL; a platelet count of >75,000/μL; a Karnofsky score of >60%; and normal kidney function (serum creatinine level, <15 mg/dL).

Patients were not given IFN-α if they had a previous diagnosis of AIDS, were pregnant, were actively addicted to drugs, had severe liver disease, or had cardiopathy or severe neuropathy.

Treatment. IFN-α was given subcutaneously in a dosage of 5 million units (MU) three times a week for 3 months, and patients who responded to this treatment continued to receive IFN-α subcutaneously at a dosage of 3 million units three times a week for an additional 9 months. The response of all patients to treatment was analyzed at 3 months, and further analysis was carried out at 12 months for those who responded initially and at 12 months after the end of therapy to assess the number of relapses. A complete response was defined as the normalization of ALT levels and clearance of HCV RNA from serum; if these criteria were not met, patients were considered nonresponders (this group included partial responders whose ALT levels had decreased by >50% from the baseline value). Zidovudine (500 mg daily) was given to those HIV-infected patients with $CD4^+$ T lymphocyte counts of <500/μL, according to the approved recommendations in Spain.

The patients were monitored monthly for the first 6 months and every 2 months thereafter, starting 2 weeks after the initiation of IFN-α therapy. Clinical findings and laboratory parameters were noted for each control. Endpoints for the study were irregular follow-up or voluntary ending of treatment; development of IFN-α-related toxicity at level 3 or higher, based on the World Health Organization score; and progression of HIV infection to AIDS.

Detection of HCV RNA. We used the Inno-LiPA (line probe assay) HCV kit (Innogenetics, Ghent, Belgium) to determine HCV genotypes. For this procedure, the highly conserved 5′-noncoding region of the HCV genome was amplified by nested PCR with two sets of universal biotinylated HCV primers. The amplified products were then hybridized on a plastic strip to immobilize oligonucleotide probes specific for HCV types and subtypes. Incubation with a solution containing streptavidine labeled with alkaline phosphatase and the addition of nitroblue tetrazolium chloride provided color to reactive bands [13].

To quantitatively detect serum HCV RNA, we used a signal amplification method based on branched oligodeoxyribonucleotides (Quantiplex HCV RNA, Chiron, Emeryville, CA), according to the manufacturer's instructions [14]. The detection limit of this test is 350,000 HCV RNA equivalents (copies) per milliliter of serum.

To determine the duration of HCV infection in chronic carriers, primary exposure was estimated to have occurred on the date of the first transfusion for blood recipients and in the year that intravenous addiction practices were begun for IDUs. The last assumption is based on previous reports that in Spain, most HCV infections in IDUs occur during the first year of intravenous drug use [15].

The value of different parameters as predictors of complete response at 12 months of IFN-α therapy was analyzed for HIV-infected patients with chronic hepatitis C. On the basis of data available from studies performed in non-HIV-infected patients with chronic hepatitis C [16–21], these variables included gender, age, route of HCV infection, duration of chronic HCV infection, baseline ALT levels, severity of liver damage, HCV genotype, and the level of HCV viremia. Moreover, since the effect of IFN-α on HCV infection could be influenced by immune status, we also investigated the predictive value of the $CD4^+$ T lymphocyte count in terms of the rate of response to treatment in HIV-infected patients.

Statistical analysis. We used the χ^2 test and the Fisher's exact test to compare categorical variables. Continuous variables were compared with use of Student's *t*-test. The association between different variables and response to IFN-α therapy was quantified with use of relative risk determinations and 95% confidence intervals. Comparisons for which $P < .05$ were considered significant. Multiple logistic regression analysis was done separately for each variable that had a predictive value with statistical significance (or near significance) in the univariate analysis. In analyzing single variables, the possible confusing effect of other covariates was tested. In the final models, only those covariates that modified the association between such variables and response to treatment were considered. Analyses were performed with use of SAS (Statistical Analysis System; SAS Institute, Cary, NC) and EpiInfo (Centers for Disease Control and Prevention, Atlanta) software packages.

Results

A total of 119 patients had been enrolled in this study up to December 1993; of these patients, 90 were infected with HIV

Table 1. Features of HIV-infected patients and non-HIV-infected patients with chronic hepatitis C.

Variable	HIV-infected patients (n = 80)	Non-HIV infected patients (n = 27)	P value
No. (%) who were male	57 (71.3)	24 (88.9)	.065
Mean age in years ± SD	29.7 ± 4.9	34.1 ± 11.8	.069
No. (%) who were IDUs	77 (96.3)	15 (55.6)	<.001
Mean estimated duration of HCV infection in years ± SD	10.1 ± 4.1	7.0 ± 2.8	.077
Mean ALT level (U/L) ± SD	229.6 ± 140.8	174.4 ± 101.7	.063
No. with a Knodell score of >10/no. with liver biopsy (%)	28/69 (40.6)	6/26 (23.1)	.113
No. infected with indicated viral genotype/no. with genotype (%)			
HCV Ib alone	37/65 (56.9)	7/21 (33.3)	.060
Multiple genotypes	28/65 (43.1)	7/21 (33.3)	.429
No. with an HCV viremia level of $>10^7$ copies/mL/no. with viremia (%)	22/53 (41.5)	6/15 (40.0)	.916

NOTE. ALT = alanine aminotransferase; HCV = hepatitis C virus; IDU = injection drug user.

and 29 were not infected with HIV. However, only 107 patients (80 who were infected with HIV and 27 who were not) completed 24 months of follow-up and thus constituted the population analyzed. Twelve patients (10 who were infected with HIV and two who were not) withdrew from the study. One of these patients withdrew voluntarily and another HIV-infected patient died of an AIDS-defining event after he had completed 10 months of treatment with IFN-α (he did not completely respond to the treatment). One HIV-infected patient was excluded after completing 3 months of treatment with IFN-α because hematologic toxicity (neutropenia and thrombopenia) developed. The remaining nine patients (seven who were infected with HIV and two who were not) withdrew because of irregular follow-up.

Information on the degree of liver damage, HCV genotype, and quantitative HCV viremia level was not complete for all the patients, since Knodell's scoring system was not used uniformly in interpretating the degree of liver damage in 12 (11 who were infected with HIV and one who was not), and pretreatment serum specimens were available for genotyping and HCV viremia determinations for only 86 patients (65 who were infected with HIV and 21 who were not) and 68 patients (53 who were infected with HIV and 15 who were not), respectively.

Table 1 shows the characteristics of both the HIV-infected patients and those who were not infected. Parenteral exposure to HCV was the most frequent feature in both groups, although it was more frequent among HIV-infected patients (P = .001). In addition, IDUs constituted the predominant proportion of patients in the HIV-infected group, while recipients of blood products predominated in the non-HIV-infected group. A comparison between these groups in terms of other variables did not yield any other statistically significant difference. However, HIV-infected patients had been infected with HCV for longer periods and had higher levels of ALT at baseline, more severe liver damage, and higher levels of circulating HCV; the presence of HCV 1b genotype and coinfection with more than one HCV genotype were also more frequent in this group. Although none of these variables achieved statistical significance when HIV-infected and non-HIV-infected patients were compared, all of them have been independently associated with a lower rate of response to treatment with IFN-α among non-HIV-infected patients with chronic hepatitis C.

The comparison between the two groups in terms of response rates to IFN therapy is shown in table 2. Three analyses were performed: the first was done at the end of a 3-month course of IFN-α therapy with 5 MU given subcutaneously three times a week (early response); the second, on completion of a 12-month course of IFN-α treatment with 3 MU given subcutaneously three times a week (late response); and the third, at 12 months of follow-up after treatment (sustained response). There were no statistically significant differences when both groups were compared, although the rates of response to IFN-α among HIV-infected persons were always lower.

Relapse rates after treatment were analyzed at 12 months of follow-up. Relapses occurred in 30.8% of HIV-infected patients and in 12.5% of non-HIV-infected patients (P = .403). However, two of the 10 patients who were not infected with HIV and had had a complete response after 12 months of IFN-α therapy were lost to follow-up and therefore could not be analyzed. Even when we hypothesized that these patients would have had a sustained response at 12 months of follow-up, the difference between the two groups did not achieve statistical significance in terms of the rate of relapses (P = .392).

To investigate whether the level of HCV viremia was affected by treatment in the patients who relapsed, additional quantitation of HCV RNA in serum was performed on seven

Table 2. Comparison of response rates to IFN-α therapy among 80 HIV-infected patients and 27 non-HIV-infected patients with chronic hepatitis C.

Type of response	No. (%) of HIV-infected patients	No. (%) of non-HIV-infected patients	P value
Early	31 (38.8)	12 (44.4)	.602
Late	26 (32.5)	10 (37.0)	.666
Sustained	18 (22.5)	7* (25.9)	.716

NOTE. Early = response at 3 months of therapy; late = response at 12 months of therapy; and sustained = continued response after 12 months of therapy.

* Two of 10 non-HIV-infected patients who had a complete response at 12 months were lost to follow-up.

samples obtained from them 1 year after the end of IFN-α therapy. None of the patients showed a significant decrease in the titer of HCV RNA when current values were compared with baseline values.

No serious side effects were seen, although one HIV-infected patient withdrew from the study before completing 3 months of IFN-α therapy because hematological toxicity developed, as mentioned previously. On the other hand, 10 HIV-infected patients (12.5%) had a profound drop (reduction of over one-half) in the $CD4^+$ lymphocyte count after therapy with IFN-α was started. In all cases, this decrease occurred between the 6th and the 14th week of therapy and was transient or partially reversed in all but three of these patients (3.8%).

For the latter three patients, the dramatic decrease in the $CD4^+$ T cell count was irreversible, even after the medication was withdrawn. It is of interest that all three were male, none had a complete response to IFN-α therapy, and two were taking zidovudine before beginning treatment and during treatment with IFN-α. The $CD4^+$ lymphocyte counts of the remaining seven patients recovered, even while IFN-α therapy was maintained in four of these patients. Determinations of serum p24 antigenemia and of the presence of HLA alleles did not yield a plausible explanation, such as enhancement of HIV replication or the presence of a particular HLA haplotype, for the induction of $CD4^+$ T lymphocytopenia.

Table 3 shows the results of univariate analysis of parameters chosen as predictors of response to IFN-α therapy in HIV-infected patients with chronic hepatitis C. Two variables were independently associated with response to therapy in these patients: a $CD4^+$ T lymphocyte count of $>500/\mu L$ (OR = 2.92; 95% CI = 1.06–8.09; P = .039) and a baseline viral load of $<10^7$ copies/mL (OR = 4.22; 95% CI = 1.16–15.36; P = .029). Females responded to treatment more frequently than did males, but this difference was not statistically significant (OR = 2.57; 95% CI = 0.94–7.04; P = .067).

Table 4 shows the results of the multiple logistic regression analysis performed for those variables that showed a predictive value with statistical significance (or near statistical significance) in the univariate analysis. The possible confounding effect of other covariates was tested by analyzing single variables, and in the final models, only those covariates that modified the association between each variable and response to treatment were considered. The $CD4^+$ T lymphocyte count, expressed as either an absolute number or a percentage, was a strong predictor of response as was (independently) the level of viremia. Females responded better to IFN-α therapy than did males, but again, the difference did not achieve statistical significance in the multivariate analysis.

Discussion

Chronic liver disease caused by HCV seems to have a more accelerated course in immunocompromised patients; it progresses to cirrhosis and liver failure in a shorter period of time in such patients [22]. Among HIV-infected patients, particularly those who have acquired HIV infection via transfusions or needle sharing during drug addiction practices, chronic hepatitis C occurs frequently and has been reported to be more severe [23]. Telfer et al. [24] reported that hemophiliacs infected with HIV are 21 times more likely to develop hepatic decompensation than are non-HIV-infected hemophiliacs. Moreover, Eyster et al. [25] reported that liver failure occurred in eight (9%) of 91 hemophiliacs who were coinfected with HCV and HIV vs. none of 58 hemophiliacs who had HIV infection alone.

In countries like Spain, where IDUs represent the largest proportion of the HIV-infected population, up to 8% of hospital admissions among HIV-infected patients are due to complications of viral liver disease and/or to hepatic decompensation (e.g., ascites, encephalopathy, gastrointestinal bleeding, or peritonitis) [6, 7]. Moreover, chronic viral liver disease represents one of the five most frequent causes of in-hospital mortality among HIV-infected patients [7, 26]. For these reasons as well as the fact that HIV-infected patients are now surviving longer, therapeutic strategies to reduce the long-term impact of chronic hepatitis C are urgently needed for persons coinfected with HIV and HCV.

Several studies have shown that in non-HIV-infected patients with chronic hepatitis C, serum ALT levels return to normal in ~40% by the end of IFN-α treatment [21, 27]. Similar results were observed among the patients without HIV infection who were included in this study. Furthermore, HIV-infected patients with chronic hepatitis C and a $CD4^+$ T lymphocyte count of $>200/\mu L$ had a complete response to treatment in an equal proportion of cases. More important, at 12 months after stopping therapy with IFN-α, relapse rates were not significantly different for HIV-infected and non-HIV-infected patients.

On the other hand, ALT levels rebounded consistently only in those patients who became seropositive for HCV RNA after completion of treatment. Most relapses occurred shortly after therapy with IFN-α was stopped, and none occurred after 3 months of follow-up. In addition, titers of HCV RNA in patients who relapsed were not significantly reduced from baseline. Thus, the virological data do not support a beneficial effect of IFN-α therapy in patients who relapse.

It is interesting that the main features of chronic hepatitis C were similar in the HIV-infected and non-HIV-infected patients in this study. However, factors associated with a poorer prognosis and lack of response to IFN-α therapy tended to be more frequent among patients in the HIV-infected group; these factors included male sex, a longer duration of HCV infection, more-severe liver damage, a predominance of HCV genotype 1b and/or coinfection by several viral genotypes, and a higher level of HCV viremia [16–21]. Despite the higher incidence of negative predictive variables among patients in the HIV-infected group, the rates of response to treatment with IFN-α were not significantly lower for these patients when compared with the rates for patients with chronic hepatitis C who were not infected with HIV. However, this finding could explain the systematic trend toward lower rates of response to IFN-α ther-

Table 3. Rates of response among HIV-infected patients with chronic hepatitis C after 12 months of IFN-α therapy, according to different predictive characteristics.

Characteristic	Total no. of patients with indicated characteristic	No. (%) who responded	RR	95% CI	*P* value
Gender					
Male	57	15 (26.3)			
Female	23	11 (47.8)	1.82	0.99–3.34	.063
Mean age in y					
<30	45	16 (35.6)			
>30	35	10 (28.6)	0.80	0.42–1.55	.508
Route of infection with HCV					
Parenteral	77	26 (33.8)			
Sexual	3	0	...	...	.547
$CD4^+$ T lymphocytes					
Absolute count ($\times 10^6$/L)					
<500	35	7 (20.0)			
>500	45	19 (42.2)	2.11	1.00–4.45	.035
Percentage of CD4 T lymphocytes					
<25	29	4 (13.8)			
>25	51	22 (43.1)	3.13	1.19–8.19	.007
Mean estimated duration of HCV infection in y					
<10	27	10 (37.1)			
>10	31	10 (32.3)	0.87	0.43–1.77	.702
Unknown	22	6 (27.3)			
Baseline ALT level (U/L)					
<200	42	11 (26.2)			
>200	38	15 (39.5)	1.51	0.79–2.87	.205
Histological evidence of liver damage (Knodell's score)					
<10	41	15 (36.6)			
>10	28	9 (32.1)	0.88	0.45–1.72	.704
Unknown	11	2 (18.2)			
Viral genotypes					
HCV 1b	37	10 (27.0)			
Other	28	8 (28.6)	1.06	0.48–2.33	.890
Unknown	15	8 (53.3)			
Coinfection with more than one genotype					
Yes	28	7 (25.0)			
No	37	11 (29.7)	1.19	0.53–2.67	.673
Unknown	15	8 (53.3)			
Baseline HCV viremia level (copies/mL)					
$>10^7$	22	4 (18.2)			
$<10^7$	31	15 (48.4)	2.66	1.02–6.94	.024
Unknown	27	7 (25.9)			

NOTE. ALT = alanine aminotransferase; HCV = hepatitis C virus.

apy at 3 and 12 months of therapy, as well as at 12 months after stopping therapy, among HIV-infected patients.

Two variables were predictors of response to therapy with IFN-α in HIV-infected patients with chronic hepatitis C. A high level of HCV viremia was a strong predictor of unresponsiveness among these patients, as it was for non-HIV-infected patients with chronic hepatitis C [20, 21, 28]. On the other hand, 42.2% of patients with $CD4^+$ T lymphocyte counts of $>500/\mu L$ responded, compared with 20.0% of those with lower $CD4^+$ T lymphocyte counts ($P = .035$). Two factors could explain this difference. First, HCV replication and the viral load in circulating blood could be enhanced as HIV-related immunosuppression progresses, as has been suggested by some preliminary studies [24, 29–31] and is true with respect to hepatitis B virus infection [32]. Thus, the knowledged negative predictive value of high levels of HCV viremia could explain the poor response to IFN-α therapy among HIV-infected patients, who are more severely immunocompromised.

On the other hand, the lower response rates to IFN-α therapy among patients with low $CD4^+$ T lymphocyte counts could reflect the fact that the efficacy of IFN-α therapy is dependent on a preserved immune system. It should be remembered that IFN-α has both direct antiviral properties and immunoregulatory properties and that the latter could be relevant in the control of chronic hepatitis C. This hypothesis is supported by corresponding information from studies of IFN-α therapy for

Table 4. Logistic regression analysis of the main predictors of response to treatment with IFN-α among HIV-infected patients with chronic hepatitis C, adjusted for other possible confounding factors.

Variable	OR	95% CI	*P* value
Gender			
Male	1		
Female	2.57	0.94–7.04	.0669
HCV viremia (RNA copies/mL)			
$\geq 10^7$	1		
$< 10^7$	4.22	1.16–15.36	.0290
CD4$^+$ T lymphocyte count ($\times 10^6$/L)			
<500	1		
≥500	2.92	1.06–8.09	.0389

Kaposi's sarcoma; these studies have shown that patients with Kaposi's sarcoma and high CD4$^+$ T lymphocyte counts also respond better to treatment than those with low CD4$^+$ T lymphocyte counts [33].

An interesting result of this study was the lower rate of response to IFN-α therapy among HIV-infected males (26.3%) than among females (47.8%), a difference that was not found to be statistically significant at the end of treatment ($P = .063$). However, this difference was statistically significant during the first 8 months of therapy, when an interim analysis showed that only 20.6% of males vs. 69% of females responded to treatment with IFN-α ($P < .01$) [34]. Although several reasons could be postulated to explain this observation (e.g., better compliance with treatment among the female patients, higher baseline CD4$^+$ lymphocyte counts, shorter duration of HCV infection, less-severe liver damage, the presence of different HCV genotypes, lower levels of HCV viremia, and lower body weights), we were not able to determine a clear explanation for this finding. In addition, some investigators have observed that in non-HIV-infected patients with chronic hepatitis C, females tend to respond better to therapy than do males [35].

In this study, the degree of liver damage and the viral genotype were not determinants of response to IFN-α therapy. This finding contrasts with that observed in studies of non-HIV-infected patients; in those studies, ALT levels normalized more frequently in patients with mild liver damage than did ALT levels in patients with fibrosis or cirrhosis [36]. Furthermore, patients infected with the HCV genotype 1b have a twofold to fourfold lower response to IFN-α therapy than do patients infected with genotypes 2 and 3 [17, 21]. Unfortunately, 43.1% of HIV-infected patients included in this study were coinfected with more than one HCV genotype, and this circumstance made it difficult to analyze the point in more detail.

Moreover, the presence of coinfection, as compared with single infection due to a single HCV genotype, did not result in a poorer response to treatment with IFN-α. In contrast with individuals who have been infected by HCV through a transfusion or by an unknown source (sporadic cases), IDUs may be exposed repeatedly to HCV-contaminated blood through needle sharing. One may thus expect a high proportion of IDUs to be coinfected with more than one HCV genotype, as occurred in our study.

Except for neutropenia and thrombopenia, which developed in one patient, no serious side effects were observed among the HIV-infected patients in this study. However, three patients (3.8%) had a dramatic decrease in the number of CD4$^+$ lymphocytes after beginning IFN-α therapy. Previous reports [37, 38] that have described a rapid decline in the number of CD4$^+$ lymphocytes in HIV-infected patients receiving therapy with IFN-α have indicated that IFN-α can induce autoantibodies to some HLA antigens, causing a profound decrease in the number of CD4$^+$ lymphocytes in HIV-infected patients with these haplotypes [37]. Although we did not observe any association to HLA antigens among our patients, this unexpected side effect should be born in mind when therapy with IFN-α for chronic hepatitis C is considered for HIV-infected patients.

Treatment with IFN-α could provide additional benefits in HIV-infected patients. For instance, the antiviral effect of the drug is not restricted only to hepatitis viruses, and several studies have confirmed that IFN-α may be useful against HIV when administered as monotherapy or in association with zidovudine [39, 40]. In this way, treatment of chronic hepatitis C could provide the additional benefit of controlling HIV infection.

In summary, as a consequence of the wide use of antiretroviral and prophylactic therapies, chronic viral liver disease, particularly that caused by HCV, has become an emerging cause of morbidity and mortality among HIV-infected IDUs and transfused patients. The longer these patients survive, the more likely it is that they will die of liver failure before they die of HIV-associated complications. Our study provides evidence that IFN-α can be as effective in the treatment of chronic hepatitis C in HIV-infected patients with >200 CD4$^+$ lymphocytes as it is in non-HIV-infected patients. Furthermore, the best candidates for treatment with IFN-α seem to be HIV-infected females with higher CD4$^+$ lymphocyte counts and lower levels of HCV viremia. Since IFN-α is an expensive drug, a cost-benefit analysis is needed before its wide use in asymptomatic HIV-infected patients with chronic hepatitis C can be recommended. In addition, the effect of the drug on CD4$^+$ T lymphocytes needs to be clarified.

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