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Management of Chronic Hepatitis C in Patients Co-Infected with HIV

Focus on Safety Considerations

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Abstract

Hepatitis C virus (HCV) infection is a significant public health problem and one of the most important causes of chronic liver disease worldwide. Co-infection with HCV and HIV occurs frequently, mainly because both viruses share the same transmission routes. In recent years, the life expectancy of patients with HIV disease has been increased due to the introduction of highly active antiretroviral therapy (HAART). Furthermore, several studies have established that HIV infection is associated with a major progression of the HCV-related liver disease. Thus, end-stage liver disease has become a leading cause of morbidity and mortality in

this population, emphasising the importance of treatment of chronic hepatitis C in HIV-infected persons.

The biological and histological benefit of interferon-α (IFNα) therapy in patients co-infected with HCV/HIV is not significantly different from that noted in similar patients without HIV when the HIV infection is adequately controlled. However, patients with low CD4+ cell counts tend to respond poorly to anti-HCV therapy.

Given the relatively low sustained virological response rate to IFN alone, the use of IFNα monotherapy has been largely abandoned in favour of combination therapy with ribavirin. In the last 2 years, IFN plus ribavirin combination therapy has been the standard care for the treatment of chronic hepatitis C. Although information on the safety and efficacy of this dual therapy in HCV/HIV co-infected patients is scarce, recent trials have reported that the combination of IFN plus ribavirin is well tolerated and feasible in patients co-infected with HCV/HIV. However, the rates of sustained virological response seem to be worse than those observed in patients without HIV infection. New IFN formulations (e.g. pegylated interferon) plus ribavirin appear to be way of the future for the treatment of chronic hepatitis C in patients both with and without HIV co-infection.

1. Co-infection with Hepatitis C Virus (HCV) and HIV

Hepatitis C virus (HCV) is a significant public health problem and one of the most important causes of chronic liver disease worldwide. It has been estimated that nearly 2% of the general population in developed countries is infected with HCV.[1,2] One of the characteristics of HCV infection is its heightened propensity to evolve towards chronic disease, which can lead to cirrhosis and, in a small but significant percentage of patients, hepatocellular carcinoma.

Co-infection with HCV and HIV occurs frequently, mainly because the viruses share the same transmission routes. Interest in the treatment of chronic hepatitis C in HIV-infected persons is increasing, since end-stage liver disease is now a leading cause of morbidity and mortality in this population. Moreover, the high risk of hepatotoxicity with anti-HIV drugs represents a new challenge in these patients. HIV co-infection is associated with major progression of the liver disease of HCV. Likewise, although less definitive, HCV infection may accelerate the progression to AIDS in HIV-infected persons.[3]

In recent years, the life expectancy of patients with HIV disease has increased because of the introduction of highly active antiretroviral therapy (HAART). Furthermore, a sustained virological response can be achieved with combination therapy with interferon (IFN) plus ribavirin, as has been shown in patients infected with HCV alone. For these reasons, it is feasible and desirable to effectively treat patients who are co-infected with HCV and HIV. Moreover, the combination of IFN plus ribavirin appears to be well tolerated, with a predictable safety profile.

1.1 Epidemiology of HCV/HIV Co-Infection

Co-infection by HCV and HIV occurs frequently, because both viruses share the same transmission routes. The risk of HCV transmission is greater for patients who acquired HIV infection through parenteral exposure than for those infected through sexual exposure. Of patients who are co-infected with HIV and HCV, approximately 80% are injectable drug users and approximately 20% are homosexual/bisexual men. Thus, the main risk group for HIV co-infection is comprised, particularly in certain countries, by individuals who use injected drugs and in such regions the number of HIV-infected patients co-infected with HCV is substantial.[3] HCV infection usually occurs within 6 months to 1 year after the commencement of injected drug use. It is esti-

mated that the prevalence of HCV infection among individuals who use injected drugs varies from 75–90%, and has been reported to be close to 100% in some series involving patients with haemophilia.[4-8]

The vertical transmission of HCV infection from mother to child appears to occur with low efficiency but may be facilitated by HIV co-infection.[9,10] The rate of perinatal transmission of HCV is 5%, but increases to 14–17% in HIV co-infected patients.[11] The risk of vertical transmission of HCV is closely related to the maternal viral load, which may be correlated with the degree of HIV-related immunosuppression.[1] Although HCV-RNA has been detected in breast milk, no transmission of HCV by this route has been reported.

Sexual transmission of HCV is rare between long-term monogamous heterosexual partners. Meisel et al.[12] and Power et al.[13] studied the incidence of HCV infection in husbands of women infected with contaminated immunoglobulin. After 20 years, only two instances of HCV transmission in 487 couples were detected. However, transmission of HCV has been linked to an increased number of sexual partners, failure to use condoms, and persons with other sexually transmitted diseases. The risk of sexual transmission of HCV is higher in male heterosexuals with high-risk sexual practices than in homosexual men.[11,14]

1.2 Comparison of HCV and HIV Virology

In addition to the fact that both HIV and HCV are major health issues, there are many important similarities between these two viral infections (table I).

One of the most important is that both are RNA viruses. HCV is classified within the *Flaviviridae* family and it is a positive single-stranded RNA virus, while HIV belong to the *Retroviridae* family and is a positive double-stranded RNA virus.

Both viruses have a great deal of heterogeneity of their genomes.[15,16] HCV has six main genotypes and at least 30 subtypes have been described.[15,17] Within these subtypes, the viruses found in an individual infected subject can also show significant differences among their sequences; these are considered quasi-species, i.e. genetic variants around a 'master sequence'.[18] Three main genotypes of HIV-1 are recognised: M (main), O (outlier),[19] and the recently described group, N.[20] There are 10 main subtypes within the M genotype. The genetic variability of both HCV and HIV results from a relatively high error rate during replication that arises from the low proof-correction capacity of their polymerases. The mutation rate of the RNA polymerase-RNA dependent of HCV is 1 per 10^4–10^5 nucleotides; this means there is one mutation for each genome that is completely transcripted.[16] In the case of HIV, the rate is quite similar, and produces a divergence in the nucleotide sequence of greater than 30% when the most distant variants are analysed. The most heterogeneous regions of both viruses are those that code the envelope of the virus, which is the most immunogenic part of the virus.[15-18]

Table I. Differences and similarities between the hepatitis C virus (HCV) and HIV

	HIV	HCV
Virus discovery	1983	1989
Number of infected individuals worldwide	≈40 000 000	≈170 000 000
Genetic material	RNA	RNA
Length of genome	10 000 nucleotides	10 000 nucleotides
Genetic variability	HIV-1 and HIV-2	6 major subtypes
	3 groups (M, N, O)	
Daily production	10^9 virions	10^{12} virions
Virion half-life	4 hours	2.7 hours
Main cell target	CD4+ T lymphocyte	Hepatocytes
Main transmission route	Sexual	Parenteral
Rate of conversion to chronic disease	100%	75%
Asymptomatic period	≈10 years	≈30 years
Main outcome predictors	CD4+ cell count, viral load	Fibrosis stage
Rate of cure with therapy	0%	50%

Classifying the virus species can have important clinical implications. The great genetic variability enables both HCV and HIV to quickly develop mechanisms to adapt to the environment, and in this way to evade immune system responses and become resistant to pharmacological attack. Distinct variants might have differences in cell tropism, virulence and sensitivity to antiviral drugs. For instance, HCV subtype 1b is associated with a worse response to

treatment with IFNα than other subtypes.[21] It is known that some subtypes are predominant in certain populations, geographic areas or particular risk groups (i.e. HCV-3 in European injected drug users).[22]

There are also important differences between the viruses. Replication of HCV takes place in the liver cell cytoplasm, and it does not integrate into the cell genome.[23,24] In contrast, HIV-RNA is transcripted to DNA by reverse transcriptase and integrates in the infected cell's genome, resulting in an integrated provirus. Thus, viral load is a major prognostic indicator in HIV, but not HCV, infection. More importantly, because of the integration of HIV into the cell genome, infection with HIV is irreversible, whereas there is the potential for HCV to be eradicated. Consequently, it is easier to cure HCV infection.

1.3 How Does HCV/HIV Co-infection Influence Clinical Progression?

1.3.1 Progression of HCV

In patients who are not co-infected with HIV, HCV infection has a variable long-term prognosis. Chronic disease develops in approximately 75% of those infected. It seems to be clear that up to 20% of HCV-infected patients will develop liver cirrhosis within 20 years of infection, and of these 5–10% will develop end-stage liver disease within 10 years. Additionally, patients with cirrhosis are at risk of developing hepatocellular carcinoma at a rate of 1–2% per year.[25] However, there are some factors that can lead to more rapidly progressive fibrosis in HCV infection (table II).

In recent years, several studies have shown that there is a faster progression of HCV-related liver disease in patients co-infected with HIV.[23,26-28] The first report in 1989 by Martin et al.[29] described a rapid evolution to cirrhosis and liver failure in three patients co-infected with HCV/HIV within 3 years of acquiring HCV infection from blood transfusions. In a subsequent retrospective analysis of sequential serum samples in a cohort of 223 patients with haemophilia, with a known date of HCV/HIV co-infection, Eyster et al.[30] found that 9% of these patients developed signs of hepatic failure 10–20 years after infection. In another study conducted in HCV-infected haemophiliacs, those who were co-infected with HIV were 21 times more likely to develop hepatic failure than those not co-infected.[31] Two Spanish studies examined the time interval to the development of liver cirrhosis, comparing patients with HCV/HIV co-infection and those with HCV infection alone. In the first study, 25% of subjects co-infected with HIV and HCV developed cirrhosis 15 years after infection, compared with only 6.5% in patients with HCV infection alone.[32] Soto et al.[33] showed that the development of cirrhosis occurred in 14.9% of co-infected patients after 6.9 years, compared with 2.6% (after 23.2 years) in patients with HCV infection alone. In liver biopsies, Bierhoff et al. and García-Samaniego et al.[34,35] also observed greater liver damage in patients co-infected with HCV/HIV than in patients with HCV alone. A recent meta-analysis[36] confirmed that there is a significantly elevated relative risk of severe liver disease in persons who are co-infected with HIV and HCV.

Table II. Prognostic factors of more rapid progressive fibrosis in hepatitis C virus infection

Excessive alcohol use
HIV infection
Age >40 years at time of infection
Hepatitis B virus co-infection
Male gender
Hepatic steatosis and/or non-alcoholic steatohepatitis
Hepatic haemosiderosis

Since the introduction of HAART has prolonged the life expectancy of the HIV-infected patient, chronic liver disease has become increasingly prevalent, and it seems destined to be an important source of mortality and morbidity in the patient co-infected with HCV/HIV.[3] In a retrospective analysis of the causes of hospital admission in a reference HIV/AIDS institution in Madrid, end-stage liver disease was diagnosed in 8.6% of 1670 hospital admissions during the last 5 years; 88.6% of cases were attributable to HCV alone or in combination with other hepatotropic viruses. Of the total in-hospital mortality during the study period, death was directly related to liver complications in 4.8% of cases, making it the fifth highest cause of death for these HIV-infected patients.[37] Darby et al.[38] found that mortality from liver disease was 16.7-fold

higher and mortality from hepatocellular carcinoma 5.6-fold higher in 1218 male haemophiliac patients co-infected with HCV/HIV compared with 4865 similar patients with haemophilia and HCV alone who were exposed to the virus between 1969 and 1985. In a Spanish case-control study, hepatocellular carcinoma occurred at a younger age and after a shorter duration of HCV infection in HIV co-infected individuals.[39] Monga et al.[40] compared morbidity and mortality among 263 patients with HIV alone, 60 patients with HCV alone and 166 patients co-infected with both viruses. Patients were followed from January 1994 to May 1998. Liver decompensation occurred in 10% of patients with HCV/HIV co-infection. In contrast, no liver-related deaths or decompensation developed in patients without co-infection. The rate of death was significantly higher in co-infected patients than in patients with HIV alone. Additionally 47% of deaths in co-infected patients were due to liver-related causes.

Why is the progression of HCV liver disease more rapid in HIV-infected patients? The immunosuppression associated with HIV significantly alters the natural history and clinical course of HCV infection. The decline in cell-mediated immunity associated with HIV infection is believed to permit greater infection and injury to hepatocytes. Woitas et al.[41] suggested that cytokine production of CD3 cells infected with HIV and HCV virus is skewed towards an anti-inflammatory Th2 response rather than the protective Th1 response seen in cells infected with HCV alone. Recent data have shown that in patients co-infected with HCV/HIV, a low CD4+ cell count is related to the rate of fibrosis progression[28] and liver failure.[30,42] This association further supports the importance of immune function in containing liver injury.

HCV RNA viral load is higher in HIV-infected patients than in immunocompetent individuals.[30,43] Thomas et al.[44] showed that the rate of viral replication in co-infected patients was eight times faster than in immunocompetent individuals, and HCV levels increased by 0.5 log each year. In addition, a greater variability in HCV sequences has been described in HIV-positive patients with a CD4+ cell count of less than 200/μL. However, the pathological significance of these findings is unclear. High HCV-RNA titres do not appear to be correlated with the extent of liver fibrosis but, on the other hand, high levels of viraemia predict a worse response to anti-HCV therapy.

Causes other than a high HCV RNA load have been suggested for the worsened natural history of liver disease in HIV co-infected patients compared with patients infected with HCV alone, including the following: a higher incidence of infection with HCV genotypes 1a and 1b, a greater incidence of infection with mixed genotypes, the use of hepatotoxic medications and alcohol abuse.[1]

1.3.2 Progression of HIV

The next question is how HCV influences HIV infection. Contradictory results about the effects of HCV infection on HIV progression have been reported.[45-49] Recently, large longitudinal studies have concluded that HCV infection is a predictor of more rapid progression to AIDS in HIV infected patients. Greub et al.[46] studied 3111 patients from the Swiss cohort study. After 4 years of follow-up, the probability of progression to a new AIDS-defining clinical event was independently associated with HCV seropositivity (hazard ratio 1.7). Another study[48] confirmed these results, showing that the progression to AIDS, wasting and death was accelerated among patients co-infected with HCV/HIV who had a CD4 cell count > 500/μL. Daar et al.[47] found that baseline HCV RNA load was significantly associated with progression to AIDS and AIDS-related death in a cohort of patients with haemophilia who were co-infected with HCV/HIV. Conversely, Sulkowski et al.[49] did not detect evidence that HCV infection altered the risk of dying, developing AIDS or responding immunologically to HAART in HIV-infected patients.

2. Effects of Antiretroviral Therapy on HCV Infection

With respect to liver disease and injury, there are two key issues related to the use of antiretroviral agents: (i) the effect of antiretroviral agents on viral hepatitis; and (ii) direct hepatotoxicity.

HIV protease inhibitors have no direct beneficial effects on HCV viral load. In fact, several studies suggest that initiation of HAART in patients with chronic hepatitis C leads to increased serum transaminase levels and HCV RNA titres for the first 3–4

months, returning to baseline levels after 12 months.[50] However, the impact of HAART on the progression of HCV liver disease is controversial. There is some evidence that co-infected patients treated with protease inhibitors have a slower rate of progression to liver fibrosis.[51] The mechanisms involved in the beneficial effects, if any, of protease inhibitors on liver fibrosis remain unknown. Increases in CD4+ cell count or changes in the intrahepatic cytokine pattern of secretion related to immune restoration have been suggested to reverse or reduce proinflammatory or profibrosing processes. Roychowdhury et al.[52] assessed the role of HAART in the progression of HCV infection in 59 patients co-infected with HCV/HIV, 75% of whom were receiving HAART. The authors concluded that HCV RNA levels and Knodell's Histological Activity Index inflammation activity scores were slightly decreased in patients co-infected with HCV/HIV who were receiving HAART. The authors concluded that HAART may play a role in slowing HCV disease progression, although there was no significant effect on fibrosis score. However hepatic cytolysis is more frequent among patients treated with long-term HAART, suggesting an increase in the risk of hepatotoxicity with long-term administration.

Another important issue is the effect of immune restoration in patients with chronic hepatitis C. It could be postulated that improvements in immunity resulting from HAART might precipitate acute inflammatory responses and alter the natural history of hepatitis C. Gavazzi et al.[53] showed that the introduction of HAART induced destruction of HCV-infected hepatocytes, followed by a tighter control of HCV replication. A Spanish study in 16 HCV/HIV co-infected patients observed that HCV viral load significantly declined after one year of successful HAART.[54]

The widespread use of HAART for the treatment of HIV infection in recent years has been accompanied by an increasing number of reports of hepatotoxicity. A recent study conducted in Spain reported hepatotoxic manifestations in nearly 14% of patients after the initiation of HAART.[55] However, severe hepatotoxicity was observed in a relatively small number of patients. Several factors are associated with the risk of drug-induced hepatotoxicity, e.g. female gender, obesity, age greater than 50 years, alcoholism, a genetic predisposition and pre-existing liver disease.[56] Recent studies confirm that liver toxicity as a result of HAART occurs more frequently in patients with chronic hepatitis.[57] Nunez et al.[58] showed that HCV genotype 3 may be an independent risk factor for the development of severe transaminase elevation following the initiation of HAART.

Many antiretroviral drugs are hepatotoxic and each antiviral agent has a different potential to cause liver toxicity. HAART-induced liver toxicity may involve both direct effects of the drugs in the liver (through mitochondrial toxicity or effects on the cytochrome P450 enzyme system), or a hypersensitivity reaction, often affecting other organs.

2.1 Hepatotoxicity of Nucleoside Reverse Transcriptase Inhibitors

Hepatotoxicity associated with nucleoside reverse transcriptase inhibitors (NRTIs) has been observed in patients receiving one or more of these drugs after more than 6 months of therapy. Hepatic failure due to zidovudine was reported in the early 1990s.[59,60] Zidovudine hepatotoxicity is characterised by abdominal pain, hypertransaminaemia, elevated triglyceride levels, hepatomegaly and lactic acidosis. Abacavir has been associated with elevated liver function tests and hypersensitivity.[61]

Some recent studies[62-64] reported that the potential toxicity of these drugs depends upon their affinity for mitochondrial polymerase gamma and, in this way, they could have a differing capacity for inducing liver toxicity. Kakuda[62] suggested the following ranking for effects on mitochondrial polymerase gamma: zalcitabine > didanosine > stavudine > lamivudine > zidovudine > abacavir. Sauleda and colleagues[64] concluded that the combination of didanosine and stavudine may increase the risk of mitochondrial toxicity.

2.2 Hepatotoxicity of Non-Nucleoside Reverse Transcriptase Inhibitors

Most of the hepatic reactions associated with non-nucleoside reverse transcriptase inhibitors (NNRTIs) are idiosyncratic. They have been associated with signs of hypersensitivity reaction, such

as rash, urticaria, respiratory distress and hypotension.[65] Nevirapine seems to be the most hepatotoxic agent, followed by efavirenz and delavirdine.[1] Nevirapine has been reported to produce hepatitis in 8–28% of HIV-infected patients, mediated by cytochrome P450 induction. It has been reported that the risk of liver toxicity in patients receiving nevirapine is correlated with the CD4+ cell count.[66] In a large retrospective study of 10 611 HIV-infected patients,[67] delavirdine was associated with the lowest rate of hepatotoxicity in patients receiving NNRTIs, and patients receiving nevirapine had the highest rate of permanent discontinuation and the only hepatic-related death occurred in this group.

2.3 Hepatotoxicity of Protease Inhibitors

All protease inhibitors inhibit cytochrome P450 3A enzymes. Servoss et al.[67] found that protease inhibitors were associated with the highest rate of hepatotoxicity compared with other HAART (NRTIs and NNRTIs) in HIV-infected patients. Of the protease inhibitors, ritonavir is the most frequently associated with hepatotoxicity. Toxicity related to ritonavir may be related to high plasma concentrations, and is more likely to occur in the setting of immune reconstitution.[57] The risk is increased when ritonavir is used in high doses (>600mg). Hyperbilirubinaemia occurs in 10% of patients treated with indinavir.[55] It has been postulated that the increased unconjugated bilirubin levels associated with indinavir use are the result of decreased uridine-59-diphosphate-glucuronosyltransferase activity. Hepatitis does not often occur in patients treated with saquinavir. However, when saquinavir is combined with ritonavir, hepatotoxicity is increased in patients with chronic hepatitis. Severe hepatotoxicity is rare with nelfinavir.

3. Treatment of Chronic Hepatitis C

The US Public Health Service/Infectious Diseases Society of America 1999 guidelines recommend treating infection with HCV as for any other opportunistic disease in patients with HIV.[68] Thus, all HIV-infected patients with chronic hepatitis C should be considered for treatment. The primary goal in the treatment of HCV should be to eradicate the virus. Secondary goals may be to improve histological damage (inflammation, necrosis, fibrosis) and to reduce either the rate of cirrhosis progression or the risk of developing hepatocellular carcinoma.

Table III. Prognostic factors predicting response to IFNα in patients with chronic hepatitis C

HCV genotype other than 1
Low level of hepatic fibrosis
Short time of infection
Low pretreatment hepatitis C virus RNA levels
Low genomic diversity
Female gender

3.1 Interferon Monotherapy

IFN was the first drug that demonstrated efficacy in the treatment of chronic hepatitis C. However, the results of monotherapy with IFN administered subcutaneously were disappointing. Regimens of IFNα 3MU three times weekly for 6 or 12 months as monotherapy achieved a sustained virological response in fewer than 20% of patients.[69,70] This rate was even lower in patients carrying HCV genotype 1. IFN retreatment, longer periods of treatment (18 months) or higher doses of IFNα failed to improve the efficacy of monotherapy, but did increase the number of adverse events. Table III shows factors that could predict a response to IFNα.

Although IFN alone has little efficacy, some studies showed no difference in the response of HCV/HIV co-infected patients compared with patients infected with HCV alone with respect to biochemical response.[26,71] A Spanish study[72] reported similar results, showing that a CD4+ cell count >500 cells/μL and an HCV viraemia level $<10^7$ copies/mL were independently associated with response in HIV-infected patients. Conversely, a comparative study[73] examined IFN as monotherapy (5MU three times weekly for 6 months) in HIV-infected patients with chronic hepatitis C and patients with HCV alone. Although the end-treatment response was similar in both groups, sustained virological response was significantly lower in co-infected patients.

3.2 Interferon/Ribavirin Combination Therapy

Ribavirin is a guanidine analogue with a broad spectrum against DNA and RNA virus. It was first

approved for treatment of respiratory syncytial virus infections in children. When ribavirin is used alone for the treatment of chronic hepatitis C, it reduces alanine aminotransferase (ALT) serum levels without significant changes in HCV viraemia. For this reason, ribavirin is administered only in combination with IFN. The addition of oral ribavirin to IFN to treat chronic hepatitis C significantly reduces the rate of relapse, improving the percentage of sustained virological response. Ribavirin may act on INFα-resistant populations of virus or on intracellular reservoirs of HCV not accessible to IFNα. However, the most likely mechanism of action is that ribavirin increases production of Th1 cytokines and decreases production of Th2 cytokines.[1]

Randomised controlled trials have shown the enhancement of the efficacy of IFNα plus ribavirin in comparison with IFN monotherapy in patients with chronic hepatitis C. Using this combination regimen, approximately 50% of naive patients achieve an end-treatment response, although sustained virological response occurs in only 33% of patients treated for 6 months and 41% of those treated for 12 months.[74] Sustained virological response is strongly related to HCV genotype, and ranged from 17–29% in patients with genotype 1, to 65–67% in those with genotypes 2 or 3 who received combination therapy for 6 or 12 months, respectively.[74,75] Poynard et al.[76] assessed 1744 treatment-naive patients with chronic hepatitis C who were included in a trial that compared 24 or 48 weeks of IFNα-2b/ribavirin treatment. Five independent basal characteristics were associated with sustained virological response after 24 weeks of treatment: HCV genotype 2 or 3, baseline HCV-RNA <3.5 million copies/mL, absent or only portal fibrosis, female gender, and age younger than 40 years. These authors propose that the most efficient strategy is to treat all patients for 24 weeks. If the HCV-RNA test at this time is positive, treatment must be stopped. If it is negative, patients with fewer than four favourable factors should be treated for a further 24 weeks.

Buti et al.[77] performed a cost-effectiveness study of the use of IFNα-2b/ribavirin in treatment-naive patients with chronic hepatitis C, and concluded that defining the duration of combination therapy by baseline genotype and HCV-RNA levels at week 24 is the best strategy for standard clinical practice. On this basis, a patient with an HCV genotype other than 1 should be treated for 24 weeks. For patients with genotype 1 who cleared HCV-RNA before week 24, the most effective strategy was 48 weeks of combination therapy. Using this strategy, life expectancy increased by 0.07–0.38 years versus other strategies.

The combination of IFN plus ribavirin is also indicated in patients with chronic hepatitis C who relapse or do not respond to interferon monotherapy. In fact, these were the first indications approved for combination therapy, and it was not until some time later that the combination of IFN plus ribavirin was approved for first-line use in treatment-naive patients. Using combination therapy, sustained virological response was achieved in 49% of patients who had relapsed with interferon monotherapy[78] and in 15–20% of those who had not responded to treatment.[79,80] It is noteworthy that 86% of patients with sustained virological response and 39% of patients who relapse or do not respond with combination treatment present histological improvement (a decrease in inflammatory score of two points).[75]

3.2.1 Treatment of HCV/HIV Co-infection

Information on the efficacy of combination therapy in patients who are co-infected with HCV/HIV is scarce. Results from some controlled trials have been reported recently. Table IV summarises these data.

Landau et al.[81] evaluated 51 HIV-infected patients with chronic hepatitis C treated for 12 months

Table IV. Trials with interferon/ribavirin combination therapy in patients co-infected with HCV/HIV

Trial	Number of patients	ETR (%)	SVR (%)
Landau et al.[81]	51	29	21
Sauleda et al.[82]	20	40	40
Nasti et al.[83]	17	31	19
Pérez-Olmeda et al.[84]	106	25	16

ETR = end of treatment response; **HCV** = hepatitis C virus; **SVR** = sustained virological response.

with IFNα-2b. Of note is that 28 patients (55%) showed histological evidence of cirrhosis. At the end of treatment, HCV-RNA was undetectable in 15 patients (29%) and sustained virological response was achieved in 21%. None of the patients with a CD4+ cell count <200 cells/μL achieved sustained virological response, suggesting that the treatment of hepatitis C in HIV co-infected patients is more likely to be effective in patients with CD4+ cell counts >200 cells/μL.

Sauleda et al.[64] conducted an open-label prospective trial in 20 patients with haemophilia who were co-infected with HIV and HCV virus and who had not previously received interferon. They were treated with IFN (3 MU three times weekly) as monotherapy in the first month in order to identify potential symptoms associated with pharmacological interactions between antiretroviral and ribavirin. After 1 month, ribavirin was added at a dosage of 800 mg/day. Patients who cleared HCV-RNA at 6 months continued therapy for a total of 12 months (including patients with genotypes 2 or 3). Eight patients (40%) achieved a sustained virological response. All patients with a sustained viral response had a decrease in HCV-RNA levels of at least 1 log per month during the first 2 months. These authors reported a similar rate of response in a group of HIV-negative patients with haemophilia.[82]

Nasti and colleagues[83] enrolled 17 patients in a controlled trial in which they received IFNα-2b (3 MU three times weekly) and ribavirin (1000–1200 mg/day) for 24 weeks. Sixteen patients completed treatment and were evaluated. At the end of treatment, HCV RNA was undetectable in 31% (five patients) but only three patients (19%) achieved a sustained virological response. In this study, all three patients who achieved a sustained viral response had CD4+ cell counts >500 cells/μL and were infected by HCV genotype 3; only one patient had low HCV viraemia at baseline.

A large randomised controlled trial involving 106 HIV-infected patients with chronic hepatitis C was recently conducted in Spain.[84] Patients were randomised to receive a standard IFNα-2b dose (3 MU three times weekly) for 6 months or induction therapy (IFNα-2b 5 MU/day for 6 weeks and then the standard dose for 6 months). Ribavirin was administered in both groups at a fixed dosage of 800 mg/day. Twenty-seven patients (25.5%) cleared HCV-RNA at the end of treatment but only 17 (16%) achieved a sustained virological response. It is noteworthy that 50% of patients with sustained virological response cleared HCV-RNA in the first month of treatment. No baseline differences in either of the treatment groups were detected. Conversely, preliminary data from an ongoing study have shown that patients receiving daily combination therapy have a higher sustained virological response than those who receive IFN three times per week.[85]

Most groups have reported no significant changes in HIV viral load or CD4+ cell counts during combination therapy with IFN/ribavirin for treatment of chronic hepatitis C in HIV-infected patients.

Two studies[86,87] assessed the efficacy of combination therapy IFN/ribavirin in HCV/HIV co-infected patients who had previously received IFN monotherapy. Sustained virological response in this group was achieved in approximately 16% of patients.

3.3 Pegylated Interferon

The addition of a polyethyleneglycol (PEG) molecule to IFNα produces an active molecule with an increased half-life. The extent of this increase depends on the size and degree of branching of the PEG molecule.[88] Two pegylated formulations have been developed. Covalent attachment of a 40kd branched chain to IFNα-2a produces PEG-IFNα-2a (Pegasys®[1]). A 12kd lineal chain added to IFNα-2b produces PEG-IFNα-2b (Peg-Intron®) [figure 1]. These new formulations need to be injected subcutaneously only once per week instead of three times per week as with standard IFN. The longer half-life of PEG-IFN may also contribute to a reduced likelihood of intermittent viral load rebound.[88]

Jessner et al.[89] reported in a recent study that initial HCV viral elimination is different from that achieved with standard IFN. It is interesting to note that after the second dose of PEG-IFN, among IFN-sensitive patients with a more than 50% decrease in viral load, sustained response was achieved in 82%.

1 Use of tradenames is for identification purposes only and does not imply endorsement.

Zeuzem et al.[90] conducted a randomised trial involving 531 patients with chronic hepatitis C to assess the efficacy of PEG-IFNα-2a compared with IFNα-2a (treatment duration was 48 weeks). Therapy with PEG-IFNα-2a was associated with a higher rate of virological response (figure 2).

Heathcote and colleagues[91] studied 271 patients with chronic hepatitis C and biopsy-proven liver cirrhosis or bridging fibrosis who had not previously received IFN. Patients were randomised to received IFNα-2a (3MU three times weekly), or PEG-IFNα-2a at a dose of 90μg or 180μg once weekly for 48 weeks. The rates of sustained virological response were 8%, 15% and 30% respectively. Additionally the proportion of patients who had a significant histological improvement was lower among the group assigned to receive standard IFN than those who received PEG-IFN at a higher dose. Pockros et al.[92] demonstrated that PEG-IFNα-2a was significantly more efficacious than standard IFN for all patients, including those with more advanced liver disease.

PEG-IFNα-2b in combination with ribavirin also showed more efficacy than standard IFN/ribavirin combination therapy, according to the results of a recent randomised study. Manns and colleagues[93] assessed the efficacy of two different regimens of PEG-INFα-2b in combination with ribavirin, compared with standard therapy with IFNα-2b plus ribavirin. The first group received PEG-IFNα-2b at a dosage of 1.5 μg/kg weekly and ribavirin at a dosage of 800 mg/day for 48 weeks, and the second group received PEG-IFNα-2b 1.5 μg/kg weekly for one month followed by 0.5 μg/kg weekly for the next 44 weeks plus ribavirin 1000–1200 mg/day. Standard IFNα-2b was administered at a dosage of 3MU three times weekly plus ribavirin 1000–1200 mg/day for 48 weeks. There were 1530 patients with chronic hepatitis C recruited in the study. Results are summarised in figure 3. The sustained virological response was significantly higher in the first (high-dose) group compared with the other two treatment arms. Moreover, the benefit of a higher dose was more apparent in patients carrying the HCV genotype 1. Histological inflammation improved in all groups. Of note is that 44% of non-responders showed some evidence of histological improvement. Genotype, baseline viral load, age and the presence

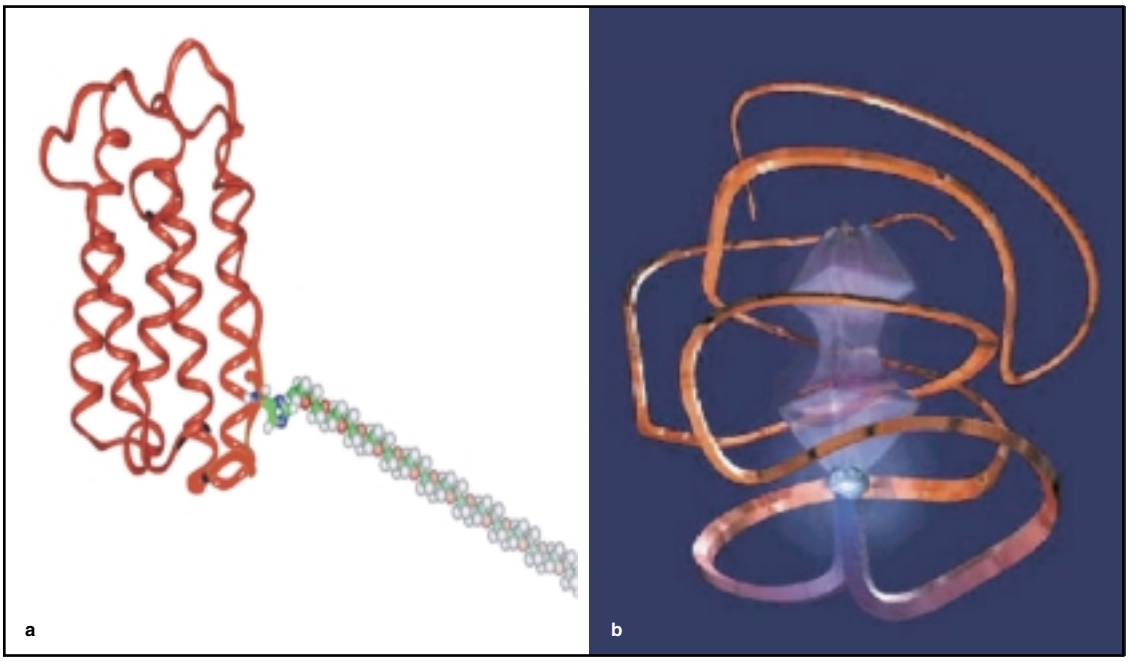

Fig. 1. (a) Pegylated interferon α-2b, and **(b)** pegylated interferon α-2a molecules.

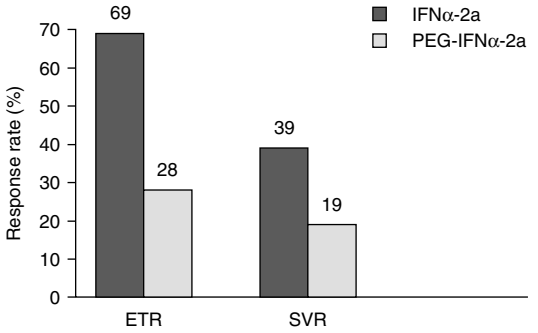

Fig. 2. Comparison of standard interferon (IFN)α-2a and pegylated interferon (PEG-IFN)α-2a as monotherapy in patients with chronic hepatitis C. **ETR** = end treatment response; **SVR** = sustained virological response.

of bridging fibrosis/cirrhosis were independent predictors of response.

3.3.1 Treatment of HCV/HIV Co-infection

Although clinical studies of treatment with PEG-IFN in the patient population co-infected with HCV/HIV have not been completed, some preliminary results have been reported recently.[94] This Spanish study included 68 HIV-infected patients with chronic hepatitis C. PEG-INFα-2b was administered at a dose of 150μg once weekly for three months and 100μg for 6 or 12 months dependent upon the HCV genotype. Patients received ribavirin at a dosage of 800 mg/day. End-treatment response was achieved in 40%, and sustained virological response in 28% of patients.

Large studies with PEG-IFN plus ribavirin are ongoing. In these settings, the APRICOT trial will include more than 700 HIV-infected patients with chronic hepatitis C. This multicentre international trial compares IFNα-2a plus ribavirin, PEG-IFNα-2a alone and PEG-IFNα-2a plus ribavirin. Perrone et al.,[95] in an interim analysis, reported an end-treatment response of 44% with PEG-IFNα-2a plus ribavirin treatment. These results seem to be worse than in individuals infected with HCV alone.

4. Adverse Effects Of Interferon and/or Ribavirin

In the treatment of chronic hepatitis C, vigilance is essential for the prevention and appropriate treatment of any adverse events that may develop. IFN therapy produces numerous adverse effects, although they are rarely dangerous for patients if adequate monitoring takes place. When ribavirin is added to IFN, additional adverse events can occur. However, the toxicity of IFN plus ribavirin is usually reversible. Complete information should be given to patients about all adverse effects that can occur during therapy with IFN plus ribavirin, preparing them for a probable decrease in their quality of life.

Most patients receiving IFN will present flu-like symptoms (fever, headache, chills, myalgias, arthralgias) that usually begin 2–4 hours after injection. These symptoms can be ameliorated or minimised by paracetamol (acetaminophen) or an NSAID taken one hour before injection, and by administering the drug in the evening. Flu-like symptoms usually occur in the first weeks of treatment and have a self-limiting course.

Haematological adverse effects can be induced by IFN or ribavirin. Thrombocytopenia and neutropenia are commonly associated with IFN. These effects are dose-related and generally reversible. When the polymorphonuclear cell count drops below 750/μL or the platelet count reaches <50 000/μL, dose reduction or discontinuation of IFN may be necessary. Granulocyte colony-stimulating factor

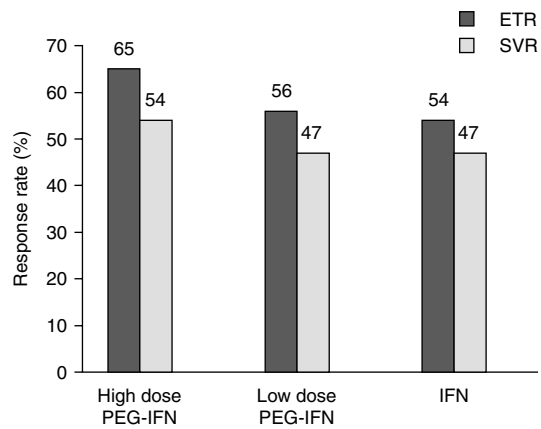

Fig. 3. Virological response comparing two different doses of pegylated interferon (PEG-IFN)α-2b plus ribavirin and standard interferon (IFN)α-2b plus ribavirin. The high-dose group received subcutaneous PEG-IFNα-2b 1.5 μg/kg weekly plus oral ribavirin 800 mg/day for 48 weeks; the low-dose group received PEG-IFNα-2b 1.5 μg/kg weekly for one month followed by 0.5 μg/kg weekly for the next 44 weeks plus ribavirin 1000–1200 mg/day. The standard IFNα-2b group received 3MU three times weekly plus ribavirin 1000–1200 mg/day for 48 weeks. **ETR** = end of treatment response; **SVR** = sustained virological response.

may be used to treat neutropenia when it is limiting therapy.

Ribavirin can produce haemolytic anaemia, which is also dose-related. The mean drop in haemoglobin level is about 2.5 g/dL and usually occurs during the first month of treatment.[75] Only in 5% of cases is the decline greater than 4 g/dL. Ribavirin-induced anaemia is usually not clinically relevant, except in patients with significant cardiovascular disease; haemoglobin levels should be carefully monitored in such patients. Dose reduction of ribavirin is recommended when the haemoglobin level drops to <11 g/dL or if it drops more than 2 g/dL since the previous control test in patients at high cardiac risk. Discontinuation of ribavirin treatment is required if haemoglobin is <8.5 g/dL in a patient without coronary risk or <12 g/dL in patients with coronary disease. Anaemia can usually be managed by reducing the ribavirin dosage, but in some patients the development of anaemia significantly limits the utility of ribavirin.

Some clinicians have used epoetin (recombinant human erythropoietin) to manage ribavirin-induced anaemia. Dieterich et al.[96] assessed the efficacy and tolerability of subcutaneous once-weekly recombinant human erythropoietin at a dose of 40 000U in patients receiving combination IFN plus ribavirin whose haemoglobin levels were below 12 g/dL. Patients were assessed after 16 weeks of therapy. Those who received epoetin had a lower mean change from baseline in their haemoglobin level and required fewer ribavirin dose modifications and drug discontinuations than the control group that did not receive epoetin. In addition, the safety profile of epoetin appears to be good, with no associated increases in adverse effects.

Depression is one of the most frequently reported reasons for discontinuation of IFN treatment. Many patients have mild changes in their behaviour or their mood, but in some cases of severe depression acts of suicide have been reported.[97,98] Therefore, all patients receiving IFN must be carefully monitored for psychiatric symptoms. Most patients can continue therapy, although dose modifications or discontinuation are sometimes required. IFN-induced depression may be treated using similar strategies that are commonly employed to treat depression in patients not receiving IFN. Additionally, psychotherapy can also be useful.

Less common adverse events include anorexia, nausea, alopecia, rashes, thyroid dysfunction, peripheral neuropathy, insomnia, ophthalmological effects and exacerbation of pre-existing psoriasis. When thyroid-stimulating hormone (TSH) levels are monitored closely, some patients show a subclinical increase in TSH. Less commonly, patients may develop sustained hyperthyroidism requiring β-adrenoceptor antagonist and/or ablative therapy. Retinopathy is a rare effect of IFN. However, a baseline fundoscopic examination is advisable before treatment in patients with diabetes mellitus or hypertension.

Ribavirin has been shown to be teratogenic in animals. Both male and female patients should use contraception until at least 6 months post-therapy.

Patients treated with combination therapy (IFN plus ribavirin) can present more frequently with adverse effects compared with those receiving IFN monotherapy, e.g. nausea, rash, dry skin, pruritus and dry cough.

4.1 Tolerability and Safety in Patients Co-infected with HCV/HIV

In patients co-infected with HCV/HIV, the tolerability and safety of IFN or IFN plus ribavirin is not different from that reported in HIV-negative patients.[64,72,75,81] The discontinuation rate due to adverse effects is similar in both groups. Conversely, Perrone et al.[95] reported a high rate of discontinuation, suggesting worse tolerability in HIV-infected patients.

One area of concern regarding the use of IFN/ribavirin combination therapy in HCV/HIV co-infected patients is whether this immunosuppressed population can tolerate the potential anaemia and decrease in leucocyte counts associated with such treatment. Ribavirin is known to inhibit the phosphorylation of zidovudine, stavudine and zalcitabine *in vitro*. This has the potential to antagonise the antiretroviral drugs anti-HIV activity *in vivo*, but clinical data have not supported this hypothesis.[61] HIV-RNA levels remained unchanged when ribavirin was combined with these antiretroviral drugs. However, the incidence of ribavirin-associated

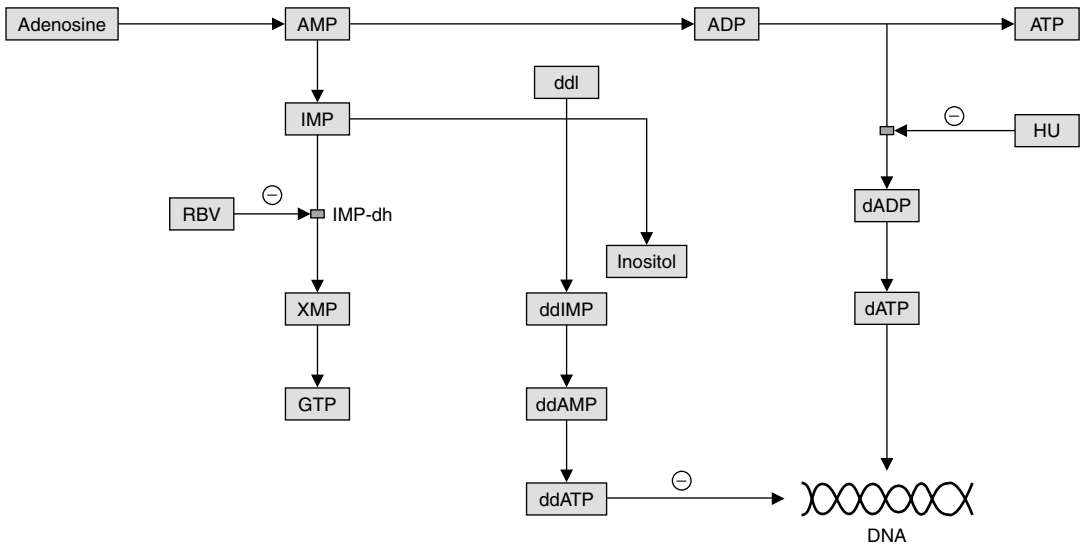

Fig. 4. Metabolic route of ribavirin (RBV) and didanosine (ddI). **ADP** = adenosine diphosphate; **AMP** = adenosine monophosphate; **ATP** = adenosine triphosphate; **GTP** = guanosine triphosphate; **HU** = hydroxyurea; **IMP** = inositol monophosphate; **XMP** = xanthosine monophosphate.

anaemia in patients with chronic hepatitis C was much higher in HCV/HIV co-infected individuals than among individuals without HIV infection.[1]

Additionally, ribavirin enhances the phosphorylation of didanosine (figure 4). An increased risk of pancreatitis and mitochondrial toxicity has been reported in patients receiving ribavirin and didanosine.[99] Sauleda et al.[64] reported a case of severe lactic acidosis in an HIV-infected patient receiving didanosine and ribavirin. This patient presented clinical, analytical and endoscopic features of compensated cirrhosis with portal hypertension. Twenty weeks after the onset of treatment, she was hospitalised because of severe lactic acidosis and died with multiorgan failure one week later. Therefore, HIV-infected patients receiving NRTIs should be carefully monitored during ribavirin treatment for the appearance of this complication.

Bacterial infection associated with granulocytopenia induced by IFN is another adverse event that must be closely monitored. Urinary tract infections, sinusitis and bronchitis are seen with increased frequency in patients receiving IFN.[1] The potential for infection is more important in immunosuppressed individuals, and any sign of infection should be promptly evaluated. During treatment with IFN in HIV-infected patients, the mean absolute number of CD4+ cells transiently decreases, returning to baseline levels after completion of treatment. However, the percentage of CD4 cells during treatment does not change or increase.[64,81] Interestingly, in a study of HIV-infected patients with chronic hepatitis C, Sauleda et al.[64] described a tendency towards a higher CD4+ cell count at the end of follow-up in the majority of patients with a sustained viral response, and they attributed this finding to the redistribution of lymphocytes previously compartmentalised within the infected liver.

5. Conclusions

HIV-related mortality has decreased dramatically with the introduction of potent antiretroviral drugs. As HCV and HIV share the same transmission routes, a relatively high rate of co-infection is observed. Co-infection is characterised by a more progressive natural course of HCV infection, leading to increased mortality from liver failure. In fact, in a Spanish study,[100] end-stage liver disease currently represents 45% of causes of in-hospital death among HIV-infected individuals. Therefore, all HIV-infected patients should be screened for HCV and considered for treatment.

5.1 Which Patients are Eligible for Treatment?

Accepted criteria for treatment of chronic hepatitis C include high ALT levels, HCV-RNA positivity in serum, and significant liver fibrosis or inflammatory activity. Patients with normal ALT levels normally have asymptomatic liver disease, mild necro-inflammatory activity with no or minimal fibrosis, and show a poor response to IFN.[101] For these reasons, available data do not recommend treatment of patients with normal transaminase levels. Many clinicians base the decision to treat on the severity of histological lesions, i.e. only patients with moderate/severe necro-inflammatory and/or fibrosis scores of F2 to F4 should be treated.

Special consideration is required in applying these general criteria to HCV/HIV co-infected patients: some degree of liver fibrosis is almost always present in these patients,[35] and the course of HCV infection is also accelerated. A proposed strategy to determine which HCV/HIV co-infected patients should be eligible for treatment may include the following criteria: persistently increased transaminase levels (more than 1.5-fold the normal values); HCV-RNA detectable in serum; good immunological status; and signs of inflammatory activity and fibrosis in liver biopsy if histological results are available. However, many patients refuse liver biopsy. In these patients, the lack of histological information should not be a contraindication for treatment.

Why is a good immunological status necessary? CD4+ cell count has been used as predictor of treatment response. When the CD4+ cell count is >500 cells/μL and the HIV viral load is undetectable, the sustained virological response rate to anti-HCV drugs in HIV-infected patients with chronic hepatitis C is similar to that observed in similar patients without HIV infection. The response rate is worse when the CD4+ cell count is 200–500 cells/μL. If the CD4 count is less than 200 cells/μL, patients should not be treated with anti-HCV drugs. In these patients, there is an important risk of opportunistic infections and the sustained virological response rate to the anti-HCV drugs is very low.[81] Clinicians should delay anti-HCV treatment in these patients until the CD4+ cell count rises, using antiretroviral therapy.

In table V, the contraindications to use of anti-HCV therapy in HCV/HIV co-infected patients are summarised. Compensated cirrhosis is not a major contraindication. Although the rate of sustained virological response to anti-HCV drugs is lower in this group of patients, a reduction in liver fibrosis and a decreased risk of developing hepatocellular carcinoma have been previously reported in patients with cirrhosis.[102] Given concerns over substance abuse, a point of controversy is whether the use of methadone is a contraindication to treating HCV/HIV co-infected patients. In our experience, patients can be treated when they have been included in a methadone programme for at least one year, and no drug consumption has occurred in this period of time.

5.2 Which Infection Should Be Treated First?

The next question is which infection to treat first? To answer this question, clinicians should consider the current stage of both diseases.

In most cases, HCV/HIV co-infected patients evaluated for HCV treatment are already on HAART or a high HIV viral load and/or low CD4+ cell count indicates that the HIV infection should be treated first. However, some problems emerge when initiating IFN plus ribavirin treatment during HAART therapy, e.g. an increased risk of anaemia, pancreatitis, lactic acidosis, and a transient decrease in the CD4+ cell count.

Treating HCV infection first has some important advantages. The risk of HAART-induced hepatotoxicity is greater in HCV/HIV co-infected patients

Table V. Contraindications to treatment of chronic hepatitis C in patients co-infected with hepatitis C virus/HIV

CD4+ cell count <200/μL
Uncontrolled HIV viral load
Ongoing substance abuse
History of severe depression or mental disorders
Haemoglobin plasma levels <13 g/dL in males and 12 g/dL in females
Platelets <75 000/μL
Granulocyte count <1500/μL
Decompensated cirrhosis
Pregnancy or refusal to use contraceptives

than in patients infected with HIV alone. Additionally, compliance with and tolerance of treatment with IFN plus ribavirin is better when patients are not receiving antiretroviral therapy.[103] In conclusion, the treatment of hepatitis C before starting HAART may be a better strategy when patients present with a good immune status.

5.3 Treatment of Hepatitis C in HCV/HIV Co-Infected Patients

Until recently, the most effective treatment for chronic hepatitis C was the combination of IFNα plus ribavirin. Now the combination of PEG-IFNα plus ribavirin seems to be the preferred option, although results of relevant clinical trials with PEG-IFNα in co-infected patients are not yet available. This regimen has shown greater efficacy than conventional IFN in patients with hepatitis C alone.[91-93] Therefore, an improved sustained virological response rate should also be achieved in co-infected individuals.

Along with other factors, the duration of treatment depends on the HCV genotype involved. To date, patients carrying HCV genotypes 2 or 3 have received 6 months of treatment (similar to that in patients with HCV alone); conversely, patients with HCV genotypes 1 or 4 should be treated for 1 year. However, high rates of relapse in patients carrying HCV genotypes 2 or 3 treated for 6 months with PEG-IFNα-2b plus ribavirin have been recently reported.[94] Therefore, extending the duration of therapy in this group of patients may be advisable. Patients with cirrhosis or advanced liver fibrosis should be treated for 48 weeks regardless of genotype and basal viral load, because these are significant adverse response predictors.[76]

Virological response must be analysed during treatment. Until now, treatment was stopped if HCV-RNA was detectable in serum by polymerase chain reaction testing at 6 months. Fried and colleagues[104] have suggested that in patients with HCV infection alone, treatment should be discontinued in patients whose HCV-RNA levels do not decline more than 2 logs or who have undetectable HCV-RNA levels at week 12. This principle may also be useful in HCV/HIV co-infected individuals, but clinical trials are needed to confirm this.

The dosage of IFN plus ribavirin for HCV/HIV co-infected patients does not differ from that used in patients without HIV infection. The ribavirin dosage must be adjusted according to patient bodyweight (10.6 mg/kg or 1000mg if bodyweight is <75kg, and 1200mg if bodyweight is >75 kg). An appropriate ribavirin dosage reduces the risk of adverse events and, on the other hand, increases the rate of sustained virological response.

5.4 Special Challenges in HCV/HIV Co-infected Patients

The optimal strategy in managing HCV/HIV co-infected patients who have either relapsed or have not responded to anti-HCV combination therapy remains unclear. Therefore, clinicians should apply the same approach as in patients not infected with HIV.

Those patients who fail to respond or relapse after IFN monotherapy may benefit from retreatment with IFN plus ribavirin for one year. There is no evidence that retreatment with IFN alone, higher dosages or prolonged treatment increase efficacy of IFN monotherapy. There are no specific recommendations for patients who do not respond to IFN plus ribavirin.

Retreatment with PEG-IFN plus ribavirin and maintenance therapy to prevent cirrhosis and hepatocellular carcinoma are currently being studied. Shiffman et al.[105] showed that maintenance IFN therapy had beneficial effects on liver histology in patients with chronic hepatitis C and persistent viraemia. In this study, 53 non-responders were randomised to receive IFN maintenance therapy or observation without treatment. In the first group, fibrosis and inflammation scores remained stable. Conversely, in the observation group, these scores deteriorated, reaching pretreatment levels. Further studies are necessary to determine which is the better strategy in these patients.

5.5 Risks and Benefits of Combination Therapy in Co-Infected Patients

Current studies recommend treating chronic hepatitis C in HIV-infected patients because HIV co-infection is associated with a major progression of the liver disease, and end-stage liver disease is a

leading cause of morbidity and mortality in this population. However, the decision to treat should be individualised in each patient, since some adverse events may cause important deleterious effects, such as lactic acidosis. In most patients, the benefits are greater than the risks, and careful monitoring can decrease the risks.

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References

1. Poles MA, Dieterich DT. Hepatitis C virus/human immunodeficiency virus coinfection: clinical management issues. Clin Infect Dis 2000; 31: 154-61
2. Fornam F, Soriano V. Chronic hepaptitis C in HIV-infected individuals. AIDS Rev 2000; 2: 168-77
3. Rodriguez-Rosado R, Garcia-Samaniego J, Soriano V. Hepatitis C, an emerging problem in HIV-infected patients. AIDS Rev 1999; 1: 22-8
4. Sulkowski M. Hepatitis C virus and HIV co-infection: a sleeping giant awakes. Hopkins HIV Rep 1999; 1: 1-5
5. Wasley A, Alter M. Epidemiology of hepatitis C: geographic differences and temporal trends. Semin Liver Dis 2000; 20: 1-16
6. Sherman K, Roustrer S, Chung R, et al. Hepatitis C: prevalence in HIV-infected patients across sectional analysis of the US ACTG. Antivir Ther 2000; 5 Suppl. 1: 64-5
7. Lauer G, Walker B. Hepatitis C virus infection. N Engl J Med 2001; 345: 41-52
8. Hagan H, Thiede H, Weiss N, et al. Sharing of drug preparation equipment as risk factor for hepatitis C. Am J Public Health 2001; 91: 42-6
9. Thomas DL, Villano SA, Riester KA, et al. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type-infected mothers: Women and Infants Transmission Study. J Infect Dis 1998; 177: 1480-8
10. Granovsky MO, Minkoff HL, Tess BH, et al. Hepatitis C virus infection in the mothers and infants cohort study. Pediatrics 1998; 102: 355-9
11. Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Morb Mortal Wkly Rep 1998; 47 (RR-19): 1-39
12. Meisel H, Reip A, Faltus B, et al. Transmission of hepatitis C virus to children and husbands by women infected with contaminated anti D-immunoglobulin. Lancet 1995; 345: 1209-11
13. Power JP, Davidson F, O´Riordau J, et al. Hepatitis C infection from anti D-immunoglobulin. Lancet 1995; 346: 372-3
14. Eyster ME, Alter HJ, Aledort LM, et al. Heterosexual cotransmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Ann Intern Med 1991; 115 (10): 764-8
15. Brechot C. Hepatitis C virus genetic variability: clinical implications. Am J Gastroenterol 1994; 84: 41-7
16. Simmonds P. Variability of hepatitis C virus. Hepatology 1995; 21: 570-83
17. Pawlotsky J, Tsakiris L, Roudot-Thoraval L, et al. Relationship between hepatitis C virus genotypes and sources of infection in patients with chronic hepatitis C. J Infect Dis 1995; 171: 1607-10
18. Domingo E, Holland J. RNA virus mutations and fitness for survival. Annu Rev Microbiol 1997; 51: 151-78
19. Myers G, Korber B, Berzofsky J, et al. A compilation and analysis of nucleic acid and amino acid sequences: Theoretical Biology and Byophysics Group. Los Alamos National Laboratory, 1997
20. Simon F, Mauclere P, Roques P, et al. Identification of a new HIV type 1 distinct from group M and group O. Nat Med 1998; 4: 1032-7
21. Zeumen S, Lee J, Roth W, et al. Mutations in the nonstructural 5A gene of European hepatitis C virus isolates and response to interferon α. Hepatology 1997; 25: 740-4
22. Nousbaum J, Pol S, Nalpas B, et al. Hepatitis C virus type 1b (II) infection in France and Italy. Ann Intern Med 1994; 122: 161-8
23. Soriano V, García-Samaniego J, Rodríguez-Rosado R, et al. Hepatitis C and HIV infection: biological, clinical and therapeutic implications. J Hepatol 1999; 31 Suppl. 1: 119-23
24. Soriano V, Rodríguez-Rosado R, García-Samaniego J. Management of chronic hepatitis C in HIV infected patients. AIDS 1999; 13: 539-46
25. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997; 112: 464-72
26. Bonacini M, Puoti M. Hepatitis C in patients with human immunodeficiency virus infection: diagnosis, natural history, meta-analysis of sexual and vertical transmission, and therapeutic issues. Arch Intern Med 2000; 160: 3365-73
27. Lessens O, Deschenes M, Steben M, et al. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. J Infect Dis 1999; 179: 1258
28. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients: The MULTIVIR Group. Hepatology 1999; 30: 1054-8
29. Martin P, Bisceglie AM, Kassianides C, et al. Rapidly progressive non-A, non-B hepatitis in patients with human immunodeficiency virus infection. Gastroenterology 1989; 97: 1559-61
30. Eyster M, Diamondstone L, Lien J, et al. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with HIV. The Multicenter Hemophilia Cohort Study. J Acquir Immune Defic Syndr 1993; 6: 602-10
31. Telfer P, Sabin C, Devereux H, et al. The progression of HCV-associated liver disease in a cohort of haemophilic patients. Br J Haematol 1994; 87: 555-61
32. Sanchez-Quijano A, Andreu J, Gavilan F, et al. Influence of human immunodeficiency virus type 1 infection on the natural course of chronic parenterally acquired hepatitis C. Eur J Clin Microbiol Infect Dis 1995; 14: 949-53
33. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol 1997; 26: 1-5
34. Bierhoff E, Fischer HP, Willsch E, et al. Liver histopathology in patients with concurrent chronic hepatitis C and HIV infection. Virchows Arch 1997; 430: 271-7
35. García-Samaniego J, Soriano V, Castilla J, et al. Influence of hepatitis C virus genotypes and HIV infection on histological severity of chronic hepatitis C. Hepatitis/HIV Spanish Study Group. Am J Gastroenterol 1997; 92: 1130-4
36. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis 2001; 33: 562-9

37. Soriano V, García-Samaniego J, Rodríguez-Rosado R, et al. Impact of chronic viral 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
38. Darby S, Ewart D, Giangrande P, et al. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood product contaminated with hepatitis C. Lancet 1997; 350: 1425-31
39. García-Samaniego J, Rodríguez M, Berenguer J, et al. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. Am J Gastroenterol 2001; 96: 179-83
40. Monga HK, Rodríguez-Barradas MC, Breaux K, et al. Hepatitis C virus infection-related morbidity and mortality among patients with human immunodeficiency virus infection. Clin Infect Dis 2001; 33: 240-7
41. Woitas RP, Rockstroh JK, Beier I, et al. Antigen-specific cytokine response to hepatitis C virus cope epitopes in HIV/hepatitis C virus-coinfected patients. AIDS 1999; 13: 1313-22
42. Makris M, Preston FE, Rosendaal FR, et al. The natural history of chronic hepatitis C in haemophiliacs. Br J Haematol 1996; 94: 746-52
43. Cribier B, Rey D, Schmitt C, et al. High hepatitis C viremia and impaired antibody response in patients coinfected with HIV. AIDS 1995; 9: 1131-6
44. Thomas DL, Shih JW, Alter HJ, et al. Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. J Infect Dis 1996; 174: 690-5
45. Piroth L, Duong M, Quantin C, et al. Does hepatitis C virus coinfection accelerate clinical and immunological evolution of HIV-infected patients? AIDS 1998; 12: 381-8
46. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival and immune recovery during antiretroviral therapy in HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort study. Lancet 2000; 356: 1800-5
47. Daar E, Lynn H, Donfield S, et al. Hepatitis C virus load is associated with human immunodeficiency virus type 1 disease progression in hemophiliacs. J Infect Dis 2001; 183: 589-95
48. Staples Jr CT, Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. Clin Infect Dis 1999; 30: 409-10
49. Sulkowski MS, Moore RD, Mehta SH, et al. Hepatitis C and progression of HIV disease. JAMA 2002; 288: 199-206
50. Rutschman OT, Negro F, Hirschel B, et al. Impact of treatment with human immunodeficiency virus (HIV) protease inhibitors on hepatitis C viremia in patients coinfected with HIV. J Infect Dis 1998; 177: 783-5
51. Benhamou I, di Martino V, Bochet M, et al. Factors affecting liver fibrosis in human immunodeficiency virus and hepatitis C virus coinfected patients: impact of protease inhibitor therapy. Hepatology 2001; 34: 283-7
52. Roychowdhury A, Lambiase L, Monteiro C, et al. The impact of HIV therapy with HAART on HCV disease in HIV/HCV coinfection [abstract 1894]. Program and abstracts of Digestive Disease Week; 2001 May 20-23; Atlanta (GA)
53. Gavazzi G, Bouchard O, Leclercq P, et al. Change in transaminases in HCV and HIV coinfected patients after HAART: differences between complete and partial virologic responders? AIDS Res Hum Retroviruses 2000; 16: 1021-3
54. Pérez-Olmeda M, García-Samaniego J, Soriano V. Hepatitis C viraemia in HIV-HCV coinfected patients having immune restoration with HAART [letter]. AIDS 2000; 14: 212
55. Rodríguez-Rosado R, García-Samaniego J, Soriano V. Hepatotoxicity after introduction of highly active antiretroviral therapy [letter]. AIDS 1998; 12: 1256
56. Bonacini M. Management issues in patients coinfected with hepatitis C virus and HIV. AIDS Read 2002; 12: 19-26
57. Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA 2000; 283: 2526-7
58. Nunez M, Rios P, Martín-Carbonero L, et al. Role of hepatitis C virus genotype in the development of severe transaminase elevation after the introduction of antiretroviral therapy. J Acquir Immune Defic Syndr 2002; 30: 65-8
59. Shriner K, Goetz MB. Sever hepatotoxicity in a patient receiving both acetaminophen and zidovudine. Am J Med 1992; 93: 94-6
60. Shintaku M, Sasu K, Shimizu T. Fulminant hepatic failure in an AIDS patient: possible zidovudine induced hepatotoxicity. Am J Gastroenterol 1993; 88: 464-6
61. Soriano V, Sulkowski M, Bergin C, et al. Care of patients with chronic hepatitis C and HIV co-infection: recommendations from an HIV-HCV international panel. AIDS 2002; 16: 813-28
62. Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. Clin Ther 2000; 22: 685-708
63. Lafeuillade A, Hittinger G, Chadapauds S. Increased mitochondrial toxicity with ribavirin in HIV-HCV coinfection. Lancet 2001; 357: 280-1
64. 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: 1035-40
65. Leitze Z, Nadeem A, Choudhary A, et al. Nevirapine-induced hepatitis treated with corticosteroids? AIDS 1998; 12: 1115-7
66. Martínez E, Blanco JL, Arnaiz J, et al. Hepatotoxicity in HIV-1 infected patients receiving nevirapine-containing antiretroviral therapy. AIDS 2001; 15: 1261-8
67. Servoss JC, Sherman KE, Robbins G, et al. Hepatotoxicity in the US: Adult AIDS Clinical Trial Group [abstract]. Gastroenterology 2001; 120: A54
68. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. USPHS/IDSA Prevention of Opportunistic Infections Working Group, Infectious Diseases Society of America. Ann Intern Med 1999; 131: 873-908
69. Poynard T, Leroy V, Cohard M, et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996; 24: 778-89
70. Carithers Jr RL, Emerson SS. Therapy of hepatitis C: meta-analysis of interferon α-2b trials. Hepatology 1997; 26 Suppl. 1: 83S-8S
71. Boyer N, Marcellin P, Degott C, et al. Recombinant interferon-alpha for chronic hepatitis C in patients positive for antibody to human immunodeficiency virus. J Infect Dis 1992; 165: 723-6
72. Soriano V, García-Samaniego J, Bravo R, et al. Interferon α for the treatment of chronic hepatitis C in patients infected with human immunodeficiency virus. Clin Infect Dis 1996; 23: 585-91
73. Coll S, Sola R, Vila MC, et al. Treatment of hepatitis C HIV-coinfected patients with interferon: controlled study [abstract 153]. In: Program and abstracts of the 50th Annual Meeting of the American Association for the Study of Liver Diseases (Dallas). Philadelphia: WB Sanders, 1999: 199A
74. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon α-2b plus ribavirin for 48 weeks or for 24 weeks versus interferon α-2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998; 352: 1426-32
75. McHutchison J, Gordon S, Schiff E, et al. Interferon α-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998; 339: 1485-92
76. Poynard T, McHutchison J, Goodman Z, et al. Is an "a la carte" combination interferon α-2b plus ribavirin regimen possible

for the first line treatment in patients with chronic hepatitis C? Hepatology 2000; 31: 211-8

77. Buti M, Casado MA, Fosbrook L, et al. Which is the most cost-effective combination therapy strategy using interferon alpha-2b plus ribavirin for naive patients with chronic hepatitis C? Clin Drug Invest 2002; 21 (1): 31-9
78. Davis GL, Esteban-Mur R, Rustgi V, et al. Recombinant interferon alpha-2b alone or in combination with ribavirin for retreatment of interferon relapse in chronic hepatitis C. N Engl J Med 1998; 339: 1493-9
79. Bacon BR, Rauscher JA, Smith-Wilkaitis NL, et al. Interferon-ribavirin combination: sustained response in previous monotherapy nonresponders. Hepatology 1999; 30: 327A
80. Morisco F, Canestrini C, Astretto S, et al. Therapeutic efficacy of reinforced vs standard combination therapy schedule (IFN α-2b + ribavirin) in chronic hepatitis C not responding or relapsing to IFN alone. Hepatology 1999; 30: 198A
81. Landau A, Batisse D, Piketty C, et al. Long-term efficacy of combination therapy with interferon-α2b and ribavirin for severe chronic hepatitis C in HIV-infected patients. AIDS 2001; 15: 1-7
82. Sauleda S, Esteban JI, Altisent C, et al. Treatment with interferon plus ribavirin in anti-HIV negative patients with congenital coagulation disorders and chronic hepatitis C. Thromb Haemost 2000; 83: 807-10
83. Nasti G, Di Gennaro G, Tavio M, et al. Chronic hepatitis C in HIV infection: feasibility and sustained efficacy of therapy with interferon α-2b and ribavirin. AIDS 2001; 15: 1783-7
84. Pérez-Olmeda M, Asensi V, Romero M, et al. Efficacy and safety of combination therapy with interferon plus ribavirin in HIV-infected patients with chronic hepatitis C [abstract]. J Hepatol 2002; 36 Suppl. 1: 108
85. Hepatitis Resource Network. Daily interferon α-2b plus ribavirin versus standard interferon tiw plus ribavirin for chronic hepatitis C in HIV-HCV coinfected patients. Dig Dis Wkly. Atlanta 2001 [2896]
86. Pérez-Olmeda M, González J, García-Samaniego J, et al. Interferon plus ribavirin in HIV-infected patients with chronic hepatitis C. J Acquir Immune Defic Syndr 1999; 22: 308-9
87. Zylbergerg H, Benhamou Y, Lagneaux J, et al. Safety and efficacy of interferon-ribavirin combination therapy in HCV-HIV coinfected subjects: an early report. Gut 2000; 47: 694-7
88. Shiffman ML. Pegylated interferons: what role will they play in the treatment of chronic hepatitis C? Curr Gastroenterol Rep 2001; 3: 30-7
89. Jessner W, Stauber R, Hackl F, et al. Effect of pegylated interferon alpha-2a on early virus elimination in patients infected with HCV genotype 1. Gastroenterology 2001; 120: A-29
90. Zeuzem S, Feinman V, Rasenack J, et al. Peginterferon α-2a in patients with chronic hepatitis C. N Engl J Med 2000; 343: 1666-72
91. Heathcote EJ, Shiffman ML, Cooksley WG, et al. Peginterferon α-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000; 343: 1673-80
92. Pockros P, Heathcote J, Schiffman ML, et al. Efficacy of pegylated interferon α-2a (PEGASYS) in randomized trials of patients with chronic hepatitis C, with and without cirrhosis: correlation of virological responses with baseline histology and genotype [abstract]. Hepatology 2000; 32: 442A
93. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon α-2b plus ribavirin compared with interferon α-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958-65
94. Pérez-Olmeda M, Romero M, Nuñez M, et al. Pegylated IFN-α2b plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. AIDS 2003; 17: 1023-8
95. Perrone C, Carrat F, Banisadr F. Ribavic: a randomized controlled trial of pegylated interferon-α2b plus ribavirin vs interferon-α2b plus ribavirin for the initial treatment of chronic hepatitis C in HIV-infected patients [abstract 183]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2002; San Diego (CA)
96. Dieterich DT, Wasserman R, Braun N, et al. Once weekly recombinant human erythropoietin facilitates optimal ribavirin dosing in hepatitis C infected patients receiving interferon alpha-2b/RBV combination therapy [abstract]. Gastroenterology 2001; 120: A64
97. Maddrey WC. Safety of combination interferon alfa 2b/ribavirin therapy in chronic hepatitis C relapsed and treatment-naive patients. Semin Liver Dis 1999; 19 Suppl 1: 67-75
98. Janssen HLA, Brouwer JF, van der Mase RC, et al. Suicide associated with alpha-interferon therapy for chronic viral hepatitis. J Hepatol 1994; 21: 241-3
99. Kakuda T, Brinkman K. Mitochondrial toxic effects of ribavirin. Lancet 2001; 357: 1802-3
100. Martín-Carbonero L, Soriano V, Valencia E, et al. Increasing impact of chronic hepatitis on hospital admissions and mortality among HIV-infected patients. AIDS Res Hum Retroviruses 2001; 17: 1467-71
101. Tassopoulos NC. Treatment of patients with chronic hepatitis C and normal ALT levels. J Hepatol 1999; 31 Suppl. 1: 193-6
102. Nishiguchi S, Shiomi S, Nakatani S, et al. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. Lancet 2001; 357: 196-7
103. García-Samaniego J, Soriano V, Miró JM, et al. Management of chronic viral hepatitis in HIV-infected patients: Spanish Consensus Conference. HIV Clin Trials 2002; 3: 99-114
104. Fried M, Shiffman M, Reddy R, et al. Peginterferon α 2a plus ribavirin for chronic hepatitis virus infection. N Engl J Med 2002; 347: 975-82
105. Shiffman ML, Hoffmann CM, Contos MJ, et al. A randomized, controlled trial of maintenance interferon therapy for patients with chronic hepatitis C virus and persistent viremia. Gastroenterology 1999; 117: 1164-72

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