Therapy of chronic hepatitis C in the setting of HIV co-infection

P. Michielsen[1], E. Bottieau[2]

(1) Division of Gastroenterology and Hepatology, University Hospital of Antwerp ; (2) Institute of Tropical Medicine, Antwerp.

Abstract

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections are major health problems world-wide. As both viruses partially share routes of transmission, co-infection is common. This is especially the case in patients infected through intravenous drug use. It has been shown that HIV accelerates HCV progression to cirrhosis. The influence of HCV infection on the natural history of HIV disease remains highly controversial. It is also known that HCV co-infection increases the risk of hepatotoxicity of Highly Active Antiretroviral Therapy (HAART). These considerations as well as the improved survival of HIV patients due to HAART leads to increasing numbers of patients undergoing assessment and treatment of HCV infection. HCV treatment should be considered in stable HIV disease. Recent data indicate that HCV treatment schedules should be similar in co-infected and HCV mono-infected individuals, with pegylated interferon combined with ribavirin. For all treatment regimens published, co-infected patients had a lower sustained viral response rate compared to HCV mono-infected patients. Similar predictive factors determine the success rate. The effect of prolonging therapy to 12 months in genotype 2/3 and to 18 months in early viral responders with genotypes 1/4 needs to be assessed in further studies. (Acta gastroenterol. belg., **2005**, 68, **86-91**).

Key words : hepatitis C, human immunodeficiency virus, co-infection, interferon, pegylated interferon, ribavirin, antiretroviral therapy.

1. Epidemiology of HCV/HIV co-infection

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection are major health problems world-wide. According to the World Health Organisation, there are currently an estimated 170 million people infected with HCV (1), and 40 million with HIV (2). Both viruses share similar routes of transmission, which explains the high number of co-infected individuals. Overall, around one third of HIV-infected persons suffer from chronic hepatitis C. Both viruses can be transmitted via contaminated blood, but HCV is approximately 10 fold more infectious by this route (3). In contrast, HIV is more infectious by sexual and perinatal routes. This explains why hepatitis C is found in 50-90% of HIV-positive intravenous drug users (4-6), but only in a minority (4-8%) of HIV-positive homosexuals.

The introduction of Highly Active Antiretroviral Therapy (HAART) has significantly improved the life expectancy of HIV-infected patients in the last few years. Unfortunately, the consequences of chronic hepatitis C have become more apparent either as a result of end-stage liver disease or as a major risk for hepatotoxicity using antiretroviral drugs. Liver disease due to HCV is now a leading cause of morbidity and mortality among HIV-infected patients in the developed world, where opportunistic infections have dramatically declined (7-9).

2. Interactions of HIV and HCV infection

2.1. *Effect of HIV on HCV progression*

Most studies have demonstrated that progression to cirrhosis is accelerated in the setting of HIV co-infection (less than 15 years in co-infected individuals in comparison with more than 30 years in HCV mono-infected patients).

In the cohort study of Soto *et al.* (10), who followed a large group of HCV mono- and HIV/HCV co-infected patients, 14.9% of co-infected patients developed cirrhosis versus only 2.6% in HCV mono-infected patients after 10 years. Sanchez-Quijano *et al.* (11) found that within 15 years of initial HCV infection, 25% of those who were co-infected with HIV developed cirrhosis compared with only 6.5% of those without HIV infection. In another study comparing a cohort of 122 HCV-infected individuals with 122 HIV/HCV co-infected patients, the impaired cell-mediated immunity in HIV infection accounts largely for this effect, although other factors such as alcohol consumption contribute equally to favour more rapid evolution to cirrhosis (12). Also hepatocellular carcinoma appears to occur at a younger age and after a shorter duration of HCV infection in co-infected individuals (13).

A recent German study has shown that potent antiretroviral therapy reduces overall mortality in co-infected patients (mostly haemophiliacs), not only by decreasing the rate of AIDS-related deaths, but also liver-related deaths, suggesting that the control of HIV infection is also beneficial for the course of HCV disease (14). However, the health benefit associated with HAART was only very marginal when such study has been conducted in settings where HCV-positive patients were mainly injection drug users (15).

Correspondence to : Prof. P. Michielsen, Division of Gastroenterology and Hepatology, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Edegem. E-mail : peter.michielsen@uza.be.

2.2. *Effect of HCV on HIV progression*

The influence of HCV infection on the natural history of HIV disease remains highly controversial. Most studies before the HAART era suggested that HCV had no influence on the course of HIV (16-18), although some of them brought contradictory results (19-22). Recent prospective longitudinal studies, conducted since the wide use of HAART, suggest that HCV is an independent risk factor for HIV disease progression (15,23-25), but this remains disputed by other cohort studies (John Hopkins Cohort and Australian HIV Database), where HIV disease outcomes do not appear to be adversely affected by HCV co-infection (26,27). In fact, several studies show an impaired CD4 recovery after HAART initiation in co-infected patients (23,27,28), but whether this poorer CD4 count response has a real clinical impact on HIV progression remains to be answered.

2.3. *Hepatotoxicity of HAART*

It is well established that the presence of HCV co-infection increases the risk of developing hepatotoxicity on HAART by roughly 2-3 fold (29,30). Overall, grade 3-4 liver toxicity (transaminase levels above 5-fold the upper limit of normal values) is seen in up to 18% of individuals receiving antiretroviral drugs (31). However, most of the time, the transaminase elevation is mild to moderate, and 90% of co-infected patients are able to take HAART without problems. Therefore, HCV infection should not prejudice the decision to initiate antiretroviral treatment.

Several mechanisms of liver toxicity have been described. The first represents a hypersensitivity reaction, often associated with other symptoms such as skin rash and fever, and occurs a few days to weeks after beginning antiretroviral therapy. This is particularly known for the non nucleoside reverse transcriptase inhibitors (NNRTI), especially nevirapine, but also for abacavir, a nucleoside reverse transcriptase inhibitor (NRTI). A second mechanism with delayed onset, typically appearing several months after beginning therapy, is limited to the liver and represents an intrinsic toxic effect of the drug, and is dose-related. This type of liver toxicity may also be due to the NNRTI, especially nevirapine, and to some protease inhibitors (PI), like ritonavir and indinavir (32). Drug-related hepatotoxicity may also be part of a general mitochondrial toxicity, attributable to some NRTI (especially stavudine and didanosine), and sometimes associated with other symptoms (neuropathy, pancreatitis, lactic acidosis,…) (33). Finally, the metabolic side effects of the PI (impaired glucose tolerance, hyperlipidemia) may cause hepatic steatosis, sometimes associated with liver enzyme elevation and even clinical hepatitis (30,34).

In addition to and beside specific drug toxicities, a new mechanism is increasingly recognised in HCV/HIV co-infected patients : the so-called “immune reconstitution syndrome”. This represents the immune-induced inflammatory reaction to an underlying (and sometimes quiescent) condition, observed a few weeks after HAART initiation (35). This phenomenon corresponds to a dramatic CD4 cell increase, and may be responsible for severe flares of hepatitis, requiring drug discontinuation. Liver biopsy confirms exacerbation of chronic hepatitis, as clearly demonstrated by Puoti and colleagues (36). In conclusion, the differential diagnosis of liver enzyme elevation in co-infected patients initiating HAART is extremely difficult, including drug toxicity, immune reconstitution syndrome, intercurrent infections/hepatitis, and other toxic factors such as alcohol. A careful diagnostic workup is required, because of its therapeutic implications.

Table 1. — **Treatment response to interferon monotherapy in HIV/HCV co-infected patients**

Trial	Year	Sustained virologic response
Boyer *et al.* (40)	1992	1/12
Marriott *et al.* (38)	1993	4/9
Marcellin *et al.* (41)	1994	3/20
Soriano *et al.* (39)	1996	18/80
Mauss *et al.* (42)	1998	5/17
Causse *et al.* (43)	2000	7/63
Prestileo *et al.* (44)	2000	1/41
		39/242 (16%)

3. Hepatitis C treatment in co-infected patients

Prior to the availability of HAART, treatment in co-infected patients was directed primarily at managing HIV-related opportunistic infections with little, if any, attempts to treat HCV infection. With the disappearance of most opportunistic infections and the resultant rise in longevity, increasing numbers of patients are undergoing assessment and treatment of HCV infection.

3.1. *Interferon-α monotherapy*

Early studies of interferon-α monotherapy suggest that responses in co-infected patients are similar to those in immune competent patients, providing the CD4+ count is well preserved (> 500/μL) (Table 1 ; 38-44). Rates of sustained virological responses (SVR) (i.e. virological response at 6 months after treatment) vary from 0% (37) to 36% (38). The largest study of interferon monotherapy (80 co-infected patients) reported SVR of 23% after 48 weeks of treatment (39).

Side-effects of interferon-α treatment

Problems include the high incidence of side effects and the possible fall in CD4+ cell count as a result of drug-induced leukopenia (45). Interferon-α therapy can induce a rapid decline in the CD4+ count in around 10% of patients with HIV infection (46). This drop usually occurs within the first 12 weeks of therapy and tends to be transient, even without stopping therapy. However, prolonged CD4 depletion has been anecdotally observed (47). A parallel increase in HIV RNA is not seen,

Table 2. — **Treatment response to interferon plus ribavirin in HIV/HCV co-infected patients**

Trial	Year	Sustained virologic response
Pérez-Olmeda *et al.* (51)	1999	5/11
Zylberberg *et al.* (52)	2000	3/21
Landau *et al.* (53)	2001	14/60
Sauleda *et al.* (54)	2001	8/20
Nasti *et al.* (55)	2001	3/17
Bochet *et al.* (56)	2001	6/30
Pérez-Olmeda *et al.* (57)	2003	17/106
		56/265 (21%)

which suggests that interferon causes a redistribution of CD4+ cells from the vascular to the tissue compartments rather than a destruction of these cells due to an increase in HIV replication (48).

3.2. *Interferon-α-ribavirin combination therapy*

The standard care of chronic hepatitis C in immune competent patients now involves the addition of ribavirin to interferon-α therapy. It has been demonstrated to reduce the rate of relapse and to double the SVR in chronic hepatitis C (49,50).

The data now available suggest that combination treatment yields a SVR of 21 % in HCV-HIV co-infected patients (Table 2 ; 51-57), which is lower than in HCV-mono-infected patients (overall SVR of nearly 40%). Factors predicting successful treatment, e.g. absence of cirrhosis and genotype 2 or 3, are the same in HIV-positive as HIV-negative patients, but in HIV-infected patients, a high CD4 cell count represents a strong predictive factor for viral eradication.

Side effects of ribavirin treatment

Ribavirin can induce severe anaemia mainly when used concomitantly with certain antiretroviral agents, particularly zidovudine (AZT). Ribavirin, a guanosine nucleoside analogue, is known to inhibit the intracellular phosphorylation of AZT and stavudine (d4T) in vitro, thus reducing the effectiveness of these drugs (58). However, to date, clinical data have not supported these in vitro observations (59,60).

Recent case reports have led to concern about the possible increased risk of pancreatitis and mitochondrial toxicity in patients taking ribavirin and didanosine, sometimes with fatal outcomes (61-63). Ribavirin enhances phosphorylation of didanosine, leading to elevation of the active product of didanosine. This inhibits not only HIV reverse transcriptase but also mitochondrial DNA polymerase α, probably the cause of the mitochondrial toxicity. In September 2002 the FDA recommended to avoid the association of didanosine and ribavirin.

3.3. *Pegylated interferon-ribavirin combination treatment* (Table 3)

The development of a new pharmacological form of interferon by the covalent link with polyethylene glycol (PEG) extends the half-life of the drug, which can be administered once weekly. The combination of peginterferon and ribavirin has been shown to allow an overall SVR of 54-60% of immune competent naïve patients in intent-to-treat analysis (64-66).

Clinical trials exploring efficacy and safety of pegylated interferon in combination with ribavirin in HCV-HIV co-infected patients have recently been published.

A Spanish study involving 68 HIV/HCV co-infected patients treated with peginterferon-α2b plus ribavirin for 12 months (genotypes 1 and 4) or 6 months (genotype 3) showed a SVR in 28% of the patients in intent-to-treat analysis. Predictors of response were genotype 3 and low viral load. Treatment discontinuation for side effects was noted in 15% (67).

Another Spanish study investigated the use of interferon-α2b 3 MU t.i.w. plus ribavirin (800-1200 mg/d in 43 HIV-HCV co-infected patients with peginterferon-α2b 100 or 150 µg/wk plus ribavirin 800-1200 mg/d for 24 weeks in genotypes 2 and 3 and 48 weeks in the other genotypes (68). SVR was 44% in de peginterferon arm, significantly higher than in de standard interferon arm (21%) ($p = 0.017$). Side effects were very frequent in both arms without statistically difference between the arms.

The French RIBAVIC study is a prospective multicentre randomised trial (69). Four hundred and sixteen HIV-HCV co-infected patients were treated with standard interferon-α2b 3MU tiw or peginterferon-α2b 1.5 µg/kg/wk plus ribavirin 800 mg/d for 48 weeks. Peginterferon-α2b showed an overall SVR of 26% in combination with ribavirin, compared with 18% for conventional interferon-α2b plus ribavirin ($p < 0.03$). Of note is that treatment had to be discontinued in 1/3 of the patients, mostly because of side effects.

The ACTG study (AIDS Clinical Trials Group) is a prospective trial in 21 US centres of 66 HIV-HCV co-infected subjects treated with 180 µg peginterferon-

Table 3. — **Treatment response to peginterferon plus ribavirin in HIV/HCV co-infected patients**

Trial	Year	Type peginterferon	Sustained virologic response
Pérez-Olmeda *et al.* (67)	2003	Peginterferon-α2b	19/68 (28%)
Laguno *et al.* (68)	2004	Peginterferon-α2b	23/52 (44%)
Carrat *et al.* (69)	2004	Peginterferon-α2b	54/205 (26%)
Chung *et al.* (70)	2004	Peginterferon-α2a	18/66 (27%)
Torriani *et al.* (71)	2004	Peginterferon-α2a	116/289 (40%)

α2a/wk plus ribavirin and 67 subjects assigned to receive 6 MU interferon-α2a tiw plus ribavirin for 48 weeks (70). SVR in peginterferon group was significantly higher compared to the standard interferon group (27 vs 12%, p = 0.03).

The APRICOT study (**A**IDS **P**egasys **R**ibavirin **I**nternational **Co**infection **T**rial) (71) is an international study including 868 HIV-HCV co-infected patients treated with peginterferon-α2a 180 µg/wk plus ribavirin 800 mg qd (arm 1), or peginterferon-α2a 180 µg/wk monotherapy (arm 2) or conventional interferon-α2a 3 MU tiw plus ribavirin 800 mg qd (arm 3) for 48 weeks. Combination of peginterferon-α2a plus ribavirin (arm 1) resulted in a SVR in 40% versus 20% in arm 2 and 12% in arm 3 ($p < 0.0001$ arm 1 vs arm 3). Independent factors associated with SVR were genotype non-1 and HCV RNA viral load < 800,000 IU/mL.

Another interesting point is that nonresponse to peginterferon-α2a plus ribavirin (defined as a less than 2 log decline in HCV RNA) after 12 weeks continuous therapy had a negative predictive value of 98% for SVR. This suggests that patients who have not had a virological response at week 12 will almost certainly not achieve a SVR at the end of follow up (71). Also in the RIBAVIC study, the negative predictive value of early virological response at week 12 was 87% (69). This is in accordance with the data in HCV mono-infected patients (65,72).

Direct comparison between the above mentioned studies is not possible as the treated populations are different. The proportion of cirrhosis in the RIBAVIC study was 40% versus only 15% in APRICOT. The results for conventional interferon/ribavirin in the RIBAVIC study were more favourable than expected.

In 2001, the Belgian Association for the Study of the Liver (BASL) started an open label multicentric study on treatment of naïve HCV-HIV co-infected patients with peginterferon-α2b 1.5 µg/kg/wk plus ribavirin 800-1200 mg/d for 52 weeks. The study was closed for new inclusions on Dec 31, 2003. Final results will be available by mid-2005.

4. Conclusions

Liver disease caused by chronic hepatitis C virus infection has become one of the leading causes of morbidity and mortality among HIV-infected patients in the developed world. The rate of co-infection is especially high among intravenous drug users. Since HCV-related liver disease progesses much faster in the setting of HIV infection and the risk of liver toxicity using antiretroviral drugs is increased in the presence of underlying chronic hepatitis C, treatment of this condition has become mandatory. Based on the currently available literature summarized in this paper, and after consulting recently published guidelines on management of HIV-HCV co-infection (31,73-76), recommendations applicable on the Belgian population were written, published elsewhere in this issue.

References

1. World Health Organisation Weekly Epidemiological Record 49, 1999.
2. World Health Organisation ; AIDS epidemic update : December 2003.
3. CARDO D.M., CULVER D.H., CIESIELSKI C.A., SRIVASTAVA P.U., MARCUS R., ABITEBALL D. *et al.* Case control study of a HIV-seroconversion in health care workers after percutaneous exposure. *N. Engl. J. Med.*, 1997, **337** : 1485-1490.
4. CDC. Prevalence of hepatitis C virus infection among clients of HIV counseling and testing sites – Connecticut, 1999. *MMWR*, 1999 (50), **27** : 577-581.
5. THOMAS D.L.S.J., ALTER H.J., VLAKOV D., COHN S., HOOVER D.R., CHEUNG L., NELSON K.E. Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. *J. Infect. Dis.*, 1996, **174** : 690-895.
6. STUBBE L., SORIANO V., ANTUNES F. *et al.* Hepatitis C in the Euro SIDA cohort of European HIV-infected patients. Prevalence and prognostic value (abstract 22261). Conference record of the 12th World AIDS Conference, Geneva, Switzerland. Geneva, Marathon Multimedia, 1998.
7. BICA I., MC GOVERN B., DHAR R., STONE D., MC GOWAN K., SCHEIB R., SNYDMAN D.R. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin. Infect. Dis.*, 2001, **32** : 492-497.
8. CACOUB P., GEFFRAY L., ROSENTHAL E., PERRONNE C., VEYSSIER P., RAGUIN G., Joint Study Group on Hepatitis C Virus of the French National Society of Internal Medicine and the French Society of Infectious Diseases (GERMVIC Study Group). Mortality among HIV-infected patients with cirrhosis or hepatocellular carcinoma due to hepatitis C virus in French Departments of Internal Medicine/Infectious Diseases in 1995 and 1997. *Clin. Infect. Dis.*, 2001, **32** : 107-1214 .
9. ROSENTHAL E., POIRÉE M., PRADIER C., PERRONNE C., SALMON-CERON D., GEFFRAY L., MYERS R.P., MORLAT P., PIALOUX G., POL S., CACOUB P., GERMIVIC JOINT STUDY GROUP. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic, 2001 study). *AIDS*, 2003, **17** : 1803-1807.
10. SATO B, SÁNCHEZ-QUIJANO A., RODRIGO L., DEL OLMO J.A., GARCIA-BENGOECHEA M., HERNANDEZ-QUERO J., REY C., ABAD M.A., RODRIGUEZ M., SALES GILABERT M., GONZALEZ F., MIRON P., CARUZ A., RELIMPIO F., TORRONTERAS R., LEAL M., LISSEN E. Impact of HIV type 1 infection on the natural course of chronic parenterally acquired hepatitis C with an unusually rapid progression to cirrhosis. *J. Hepatol.*, 1997, **26** : 1-5.
11. SÁNCHEZ-QUIJANO A., ANDREU J., GAVILAN F., LUQUE F., ABAD M.A., SOTO B., MUNOZ J., AZNAR J.M., LEAL M., LISSEN E. Influence of HIV type 1 infection on the natural course of chronic parenterally acquired hepatitis C. *Eur. J. Clin. Microbiol. Infec. Dis.*, 1995, **14** : 949-953.
12. BENHAMOU Y.B.M., DI MARTINO V., CHARLOTTE F., AZIRIA F., COUTELHER A., VIDAD M., BRICAIRE F., OPDON P., KATHAMA C., POYNARD T. Liver fibrosis progression and hepatitis C virus co-infected patients. *Hepatology*, 1999, **30** : 1054-1058.
13. GARCÍA-SAMANIEGO J., RODRÍGUEZ M., BERENGUER J., RODRÍGUEZ-ROSADO R., CARBÓ J., ASENSI V., SORIANO V. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am. J. Gastroenterol.*, 2001, **96** : 179-183.
14. QURISHI N., KREUZBERG C., LÜCHTERS G., EFFENBERGER W., KUPFER B., SAUERBRUCH T., ROCKSTROH J.K., SPENGLER U. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet*, 2003, **362** : 1708-13.
15. LEIN M.B., LALONDE R.G., SUISSA S. The impact of Hepatitis C virus coinfection on HIV progression before and after Highly Active Antiretroviral Therapy. *J. Acq. Imm. Def. Syndr.*, 2003, **33** : 365-372 .
16. DORRUCCI M., PEZZOTTI P., PHILLIPS A.N., LEPRI A.C., REZZA G. Coinfection of hepatitis C virus with human immunodeficiency virus and progression to AIDS. *J. Infect. Dis.*, 1995, **172** : 1503-1508.
17. STAPLES C.T., RIMBAUD D., DUDAS D. Hepatitis C in the the HIV (Human Immunodeficiency Virus) Atlanta VA (Veterans Affairs Medical Center) Cohort Study (HAVACS) : The effect of coinfection on survival. *Clin. Infect. Dis.*, 1999, **29** : 150-154.
18. WRIGHT T.L., HOLLANDER H., PU X., HELD M.J., LIPSON P., QUAN S., POLITO A., THALER M.M., BACCHETTI P., SCHARSCHMIDT B.F. Hepatitis C in HIV-infected patients with and without AIDS : prevalence and relationship to patient survival. *Hepatology*, 1994, **20** : 1152-1155.
19. PIROTH L., DUONG M., QUANTIN C. Does HCV co-infection accelerate clinical and immunological evolution of HIV-infected patients ? *AIDS*, 1998, **12** : 381-388.

20. SABIN C., TELFER P., PHILIPS A., BHAGANI S., LEE C. The association between HCV genotype and HIV disease progression in a cohort of hemophiliacs. *J. Infect. Dis.*, 1997, **175** : 164-168.
21. LESENS O., DESCHENES M., STEBEN M., BELANGER G., TSOUKS C. Hepatitis C virus is relate to progessive liver disease in HIV-positive hemopiliacs and should be treated as an opportunistic infection. *J. Infect. Dis.*, 1999, **179** : 1254-1258.
22. TEDALDI E.M., BAKER R.K., MOORMAN A.C., ALZOLA C.F., FURHRER J., McCABE R.E., WOOD K.C., HOLMBERG S.D., HIV OUTPATIENT STUDY (HOPS) INVESTIGATORS**.** Influence of coinfection with HCV on morbidity and mortality due to HIV infection in the era of HAART. *Clin. Infect. Dis.*, 2003, **36** : 363-367 .
23. GREUB G., LEDERGERBER B., BATTEGAY M., GROB P., PERRIN L., FURRER H., BURGISSER P., ERB P., BOGGIAN K., PIFFARETTI J.C., HIRSCHEL B., JANIN P., FRANCIOLI P., FLEPP M., TELENTI A. Clinical progression and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection. *Lancet*, 2000, **336** : 1800-1805.
24. SORIANO V., MARTÍN J.C., GONZÁLEZ-LAHOZ J. HIV-1 progression in hepatitis C-infected drug users. *Lancet*, 2001, **357** : 1361-1362.
25. DE LUCA A, BUGARINI R, LEPRI A. Coinfection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naïve HIV-infected subjects. *Arch. Intern. Med.*, 2000, **162** : 2125-2132.
26. SULKOWSKI M., MOORE R., MEHTA S., CHAISSON R., THOMAS D. Hepatitis C and progression of HIV disease. *JAMA*, 2002, **288** : 199-206.
27. LINCOLN D., PETOUMENOS K., DORE G.J., Australian HIV Observational Database. HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy. *HIV Med.*, 2003, **4** : 241-249.
28. MACIAS J., MELGUIZO I., FERNANDEZ-RIVERA F. Mortality due to liver failure and impact on survival of hepatitis virus infections in HIV-infected patients receiving potent antiretroviral therapy. *Eur. J. Clin. Microbiol. Infect. Dis.*, 2002, **21** : 775-781.
29. DEN BRINKER M, WIT F, WERTHEIM-VAN DILLEN P. Hepatitis B and hepatitis C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*, 2000, **14** : 2895-2902.
30. SULKOWSKI M., THOMAS D., CHAISSON R., MOORE R. Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis C or B virus infection. *JAMA*, 2000, **283** : 74-80.
31. SORIANO V., MIRO J.M., GARCIA-SAMANIEGO J., TORRE-CISNEROS J., NUÑEZ M. *et al.* Consensus conference on chronic viral hepatitis and HIV infection : updated Spanish recommendations. *J. Viral Hep.*, 2004, **11** : 2-17.
32. SULKOWSKI M., THOMAS D., MEHTA S., CHAISSON R., MOORE R. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy : role of hepatitis C and B infections. *Hepatology*, 2002, **35** : 182-189.
33. SAVES M., VANDENTORREN S., DAUCOURT V. Severe hepatic cytolysis : incidence and risk factors in patients treated by antiretroviral combinations. Aquitaine Cohort, France 1996-1998. *AIDS*, 1999, **13** : F115-F121.
34. WIT F., WEVERLING G., WEEL J., JURRIANS S., LANGE J. Incidence and risk factors for severe hepatotoxicity associated with antireroviral combination therapy. *J. Infect. Dis.*, 2002, **186** : 23-31.
35. JOHN M., FLEXMAR J., FRENCH M. Hepatitis C virus-associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors : an immune restoration disease ? *AIDS*, 1998, **12** : 2289-2293.
36. PUOTI M., TORTI C., RIPAMONTI D., CASTELLI F., ZALTRON S., GROB P., PERRIN L., FURRER H., BURGISSER P., ERB P., BOGGIAN K., PIFFARETTI J.C., HIRSCHEL B., JANIN P., FRANCIOLI P., FLEPP M., TELENTI A. Severe hepatotoxicity during combination antiretroviral treatment : incidence, liver histology, and outcome. *J. AIDS*, 2003, **32** : 259-267.
37. POL S., TRINH THI N., THIERS V., JAFFREDO F., CARNOT F., LAMORTHE B., ZYLBERBERG H., BERTHELOT P., BRECHOT C., NALPAS B. Chronic hepatitis C of drug users : influence of HIV-infection. *Hepatology*, 1995, **22** : 340A.
38. MARRIOTT E., NAVAS S., DEL ROMERO J., GARCIA S., CASTILLO I., QUIROGA J.A., CARRENO V. Treatment with recombinant alfa-interferon of chronic hepatitis C in ani-HIV-positive patients. *J. Med. Virol.*, 1993, **40** : 107-111.
39. SORIANO V., GARCÍA-SAMANIEGO J., BRAVO R., GONZALEZ J., CASTRO A., CASTILLA J., MARTINEZ-ODRIOZOLA P., COLMENERO M., CARBALLO E., SUAREZ D., RODRIGUEZ-PINERO F.J., MORENO A., DEL ROMERO J., PEDREIRA J., GONZALEZ-LAHOZ J. Interferon alpha for the treatment of chronic hepatitis C in patients infected with human immunodeficiency virus. *Clin. Infect. Dis.*, 1996, **23** : 585-691.
40. BOYER N., MARCELLIN P., DEGOTT C., DEGOS F., SAIMOT A.G., ERLINGER S., BENHAMOU J.P. Recombinant interferon-alpha for chronic hepatitis C in patients positive for antibody to HIV. *J. Infect. Dis.*, 1992, **165** : 723-726.
41. MARCELLIN P., MARTINOT-PEIGNOUX M., ELIAS A., BRANGER M., COURTOIS F., LEVEL R., ERLINGER S., BENHAMOU J.P. HCV viremia in HIV-seronegative and seropositive patients with indeterminate HCV recombinant immunoblot assay. *J. Infect. Dis.*, 1994, **170** : 933-935.
42. MAUSS S., KLINKER H., ULMER A., WILLERS R., WEISSBRICH B., ALBRECHT H., HAUSSINGER D., JABLONOWSKI H. Response to treatment of chronic hepatitis C with interferon alpha in patients infected with HIV-1 is associated with higher CD4+ cell count. *Infection*, 1998, **26** : 16-19.
43. CAUSSE X., PAYEN J., IZOPET J., BABANY G., GIRARDIN M. Does HIV infection influence the response of chronic hepatitis C to interferon treatment ? *J. Hepatol.*, 2000, 1003-1010.
44. PRESTILEO T., MAZZOLA G., DI LORENZO F., COLLETTI P., VITALE F., FERRARO D., DI STEFANO R., CAMMA C., CRAXI A. Response-adjusted alpha-interferon therapy for chronic hepatitis C in HIV-infected patients. *Int. J. Antimicrob. Agents*, 2000, **16** : 373-378.
45. VENTO S., DI PERRI G., CRUCIANI M., GAROFANO T., CONCIA E., BASSETTI D. Rapid decline of CD4+ cells after interferon alpha treatment in HIV-1 infection. *Lancet*, 1993, **341** : 958-959.
46. CALLENS S., BOTTIEAU E., MICHIELSEN P., COLEBUNDERS R. Pegylated interferon alpha-2b plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. *AIDS*, 2004, **18** : 131 (letter).
47. SORIANO V., BRAVO R., GARCÍA-SAMANIEGO J., *et al.* CD4+ T-lymphopenia in HIV-infected patients receiving interferon therapy for chronic hepatitis C. *AIDS*, 1994, **8** : 1621-1622.
48. SORIANO V., GARCÍA-SAMANIEGO J., RODRIGUEZ-ROSADO R., GONZALEZ J., PEDREIRA J. Hepatitis C and HIV infection : biological, clinical and therapeutic implications. *J. Hepatol.*, 1999, **31** (Suppl. 1) : 119-123.
49. McHUTCHISON J.G., GORDON S.C., SCHIFF E.R., SHIFFMAN M.L., LEE W.M., RUSTGI V.K., GOODMAN Z.D., LING M.-H., CORT S., ALBRECHT J.K., HEPATITIS INTERVENTIONAL THERAPY GROUP. Interferon alpha-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N. Engl. J. Med.*, 1998, **339** : 1485-1492.
50. POYNARD T., MARCELLIN P., LEE S.S., NIEDERAU C., MINUK G.S., IDEO G., BAIN V., HEATHCOTE J., ZEUZEM S., TREPO C., ALBRECHT J., INTERNATIONAL HEPATITIS INTERVENTIONAL THERAPY GROUP. Randomised trial of interferon α2b plus ribavirin for 48 weeks or for 24 weeks versus interferon α2b plus placebo for treatment of chronic infection with hepatitis C virus. *Lancet*, 1998, **352** : 1426-1432..
51. PÉREZ-OLMEDA M., GONZÁLEZ J., GARCÍA-SAMANIEGO J., ARRIBAS J., PEÑA J., SORIANO V. Interferon plus ribavirin in HIV-infected patients with chronic hepatitis C. *J. AIDS*, 1999, **22** : 308-309.
52. ZYLBERBERG H., BENHAMOU Y., LAGNEAU J.L., LANDAU A., CHAIX M.-L., FONTAINE H., BOCHET M., POYNARD T., KATLAMA C., PIALOUX G., BRÉCHOT C., POL S. Safety and efficacy of interferon-ribavirin combination therapy in HCV-HIV coinfected subjects : an early report. *Gut*, 2000, **47** : 694-697.
53. LANDAU A., BATISSE D., PIKETTY C., DUONG VAN HUYEN J.P., BLOCH F., BELEC L., BRUNEVAL P., WEISS L., JIAN R., KAZATCHKINE M.D. Long-term effcacy of combination therapy with interferon alpha-2b and ribavirin for severe chronic hepatitis C in HIV-infected patients. *AIDS*, 2001, **15** : 1149-1155.
54. SAULEDA S., JUÁREZ A., ESTEBAN J.I., ALTISENT C., RUIZ I, PUIG L., ESTEBAN R., GUARDIA J. Interferon and ribavirin combination therapy for chronic hepatitis C in human immunodeficiency virus-infected patients with congenital coagulation disorders. *Hepatology*, 2001, **34** : 1035-1040.
55. NASTI G., DI GENNARO G., TAVIO M., CADORIN L., TEDESCHI R.M., TALAMINI R., CARBONE A., TIRELLI U. Chronic hepatitis C in HIV infection : feasibility and sustained efficacy of therapy with interferon-alfa-2b and ribavirin. *AIDS*, 2001, **15** : 1783-1787.
56. BOCHET M., DE TORRES M., VALANTAN M. *et al.* Efficacy and tolerance of interferon plus ribavirin for chronic hepatitis C in HIV-infected patients. 8th CROI 2001, Chicago, Abstract 574.
57. PÉREZ-OLMEDA M., SORIANO V., ASENSI V., MORALES D., ROMERO M., OCHOA, SANCHEZ-MONTERO F., SANTIN M., GUARDIOLA J., BLANCH J., NUNEZ M., JIMENEZ, NACHER I., GÁRCIA-SAMANIEGO J., The HCV/HIV Spanish Study Group. Treatment of chronic hepatitis C in HIV-infected patients with interferon alpha-2b plus ribavirin. *AIDS Res. Hum. Retroviruses*, 2003, **19** : 1083-1089.
58. VOGT M.W., HARTSHORN K.L., FURMAN P.A., CHOU T.C., FYFE J.A., COLEMAN L.A., CRUMPACKER C., SCHOOLEY R.T.,

HIRSCH M.S. Ribavirin antagonizes the effect of azidothymidine on HIV replication. *Science*, 1987, **235** : 1376-1379.
59. MORSICA G., DE BONA A., UBERTI C., SITIA G., FINAZZI R., LAZZARIN A. Ribavirin therapy for chronic hepatitis C in HIV-infected patients. *AIDS*, 2000, **14** : 1656-1658.
60. LANDAU A., BATISSE D., PIKETTY C., JIAN R., KAZATCHKINE M. Lack of interference between ribavirin and nucleoside analogues in HIV/HCV coinfected individuals undergoing concomitant anti-retroviral and anti-HCV combination therapy. *AIDS*, 2000, **14** : 1857-1858.
61. LAFEUILLADE A., HITTINGER G., CHAPAUDAUD S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. *Lancet*, 2001, **357** : 1803.
62. KAKUDA T., BRINKMAN K. Mitochondrial toxic effects of ribavirin. *Lancet*, 2001, **357** : 1802-1803.
63. SALMON-CÉRON D., CHAUVELOT-MOACHON J., ABAC S., SILBERMANN B., SOGNI P. Mitochondrial toxic effects of ribavirin. *Lancet*, 2001, **357** : 1803.
64. MANNS M.P., McHUTCHISON J.G., GORDON S.C., RUSTGI V.K., SHIFFMAN M., REINDOLLAR R., GOODMAN Z.D., KOURY K., LING M.-H., ALBRECHT J.K., INTERNATIONAL HEPATITIS INTERVENTIONAL THERAPY GROUP. Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C : a randomised trial. *Lancet*, 2001, **358** : 958-965..
65. FRIED M.W., SHIFFMAN M., REDDY K.R., SMITH C., MARINOS G., GONÇALEZ F.R.Jr., HÄUSSINGER D., DIAGO M., CAROSI G., DHUMEAUX D., CRAXÍ A., LIN A., HOFFMAN J., YU J., Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N. Engl. J. Med.*, 2002, **347** : 975-982.
66. HADZIYANNIS S.J., SETTE H.Jr., MORGAN T.R., BALAN V., DIAGO M., MARCELLIN P., RAMADORI G., BODENHEIMER H. Jr., BERNSTEIN D., RIZZETTO M., ZEUZEM S., POCKROS P.J., LIN A., ACKRILL A.M., PEGASYS INTERNATIONAL STUDY GROUP. Peginterferon alfa-2a and ribavirin combination treatment in chronic hepatitis C : randomized study of the effect of treatment duration and ribavirin dose. *Ann. Intern. Med.*, 2004, **140** : 346-355 .
67. PÉREZ-OLMEDA M., NUNEZ M., ROMERO M., GONZALEZ J., CASTRO A., ARRIBA, PEDREIRA J., BARREIRO P., GÁRCIA-SAMANIEGO J., MARTIN-CARBONERO L., JIMENEZ-NACHER I., SORIANO V. Pegylated IFN-alpha2b plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. *AIDS*, 2003, **17** : 1023-1028.
68. LAGUNO M., MURILLAS J., BLANCO J.L., MARTINEZ E., MIQUEL R., SANCHEZ-TAPIAS J.M., BARGALLO X., GARCIA-CRIADO A., DE LAZZARI E., LARROUSSE M., LEO A., LONCA M., MILINCOVIC A., GATELL J.M., MALLOLAS J. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS*, 2004, **18** : F27-F36.
69. CARRAT F, BANI-SADR F, POL S, ROSENTHAL E, LUNEL-FABIANI F, BENZEKRI A, MORAND P, GOUJARD C, PIALOUX G, PIROTH L, SALMON-CERON D, DEGOTT C, CACOUB P, PERRONNE C, ANRS HCO2 RIBAVIC STUDY TEAM. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients : a randomized controlled trial. *JAMA*, 2004, **292** : 2839-2848.
70. CHUNG R.T., ANDERSEN J., VOLBERDING P., ROBBINS G.K., LIU T., SHERMAN K.E., PETERS M.G., KOZIEL M.J., BHAN A.K., ALSTON B., COLQUHOUN D., NEVIN T., HARB G., VAN DER HORST C, The AIDS Clinical Trials Group A5071 Study Team. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N. Engl. J. Med.*, 2004, **351** : 451-459.
71. TORRIANI F.J., RODIGUEZ-TORRES M., ROCKSTROH J.K., LISSEN E., GONZALEZ-GARCÍA J., LAZZARIN A., CAROSI G., SASADEUSZ J., KATLAMA C., MONTANER J., SETTE H. JR., PASSE S., DE PAMPHILIS J., DUFF F., SCHRENCK U.M., DIETERICH D.T., The APRICOT Study Group. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N. Engl. J. Med.*, 2004, **351** : 438-450.
72. DAVIS G.L., WONG J.B., McHUTCHISON J.G., MANNS M.P., HARVEY J., ALBRECHT J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology*, 2003, **38** : 645-652.
73. SORIANO V., PUOTI M., SULKOWSKI M., MAUSS S., CACOUB P., CARGNEL A., DIETERICH D., HATZAKIS A., ROCKSTROH J. Care of patients with hepatitis C and HIV co-infection. *AIDS*, 2004, **18** : 1-12.
74. NELSON M.R., MATTHEWS G., BROOK M.G., MAIN J., The British HIV association. BHIVA guidelines : coinfection with HIV and chronic hepatitis C virus. *HIV Medicine*, 2003, **4** : 52-62.
75. RUYS T.A., REESINK H.W., LANGE J.M.A. Coïnfectie met hepatitis-C-virus en HIV. *Ned. Tijdschr. Geneesk.*, 2003, **147** : 2056-2060.
76. STRADER D.B., WRIGHT T., THOMAS D.L., SEEFF L.B. Diagnosis, management, and treatment of hepatitis C. *Hepatology*, 2004, **39** : 1147-71.