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# HIV-HCV RNA loads and liver failure in coinfected patients with coagulopathy

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ABSTRACT

***Background and Objective.*** **The aim of this study was to measure contemporaneously HCV-RNA load, HIV-RNA load and CD4+ lymphocytes count in HCV/HIV coinfected patients with coagulopathy and to examine the relationship between these parameters and the liver failure.**

***Design and Methods.*** **A cross-sectional study was performed on 54 patients with severe coagulopathy: 39 HCV/HIV coinfected and 15 HCV+/HIV- comparable for age and HCV exposure time. HCV-RNA and HIV-RNA load, CD4+ lymphocytes count, biochemical and ultrasonographic parameters were evaluated at the time of entry to the study.**

***Results.*** **Mean HCV-RNA load was significantly higher in coinfected patients (643,872±717,687 copies/mL) than in HCV+/HIV- (mean 161,573±276,896 copies/mL) ($p$ = 0.01). The 39 HCV/HIV coinfected patients had a mean HIV-RNA load of 205,913±456,311 copies/mL (range 4,000-2,500,000) and a mean CD4+ lymphocyte count of 206.5±171/μL (range 5-693). Five of the 39 (12.8%) coinfected patients had liver failure. In these five patients the mean HCV-RNA load (770,200±996,426 copies/mL) was high but not significantly different from that in the 34 HCV+/HIV+ patients (623,496±682,239 copies/mL) without liver failure ($p$ = 1.0). Coinfected patients with liver failure had a significantly higher HIV-RNA load (mean 764,599±978,542 copies/mL) and lower CD4+ lymphocyte count (mean 52.6±55.6/μL) than those observed in coinfected patients without liver failure ($p$ = 0.007 and $p$ = 0.03, respectively). A significant inverse correlation was found between CD4+ lymphocyte count and HIV-RNA load (r = –0.37, $p$ = 0.01).**

***Interpretations and Conclusions.*** **HCV-RNA load is significantly higher in HIV+ than in HIV- patients with coagulopathy. Liver failure was found only in the the HCV/HIV coinfected patients with severe immunodepression, expressed either by low CD4+ lymphocyte count or by high HIV-RNA load.**


Key words: HIV-RNA load, HCV-RNA load, liver failure, coinfection, coagulopathic patients

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Infection with human immunodeficiency virus (HIV) seems to accelerate the natural course of HCV infection, increasing the risk of liver failure;[1-4] HCV/HIV coinfection is frequent in intravenous drug users and transfused hemophiliacs.[5]

Early and self administration of clotting factor concentrates, a practice which began in 1970, has resulted in patients with coagulopathy having a longer and better quality of life, due to the rapid resolution of bleeding episodes. Before the use of virucidal methods in the processing of factor concentrates, over 50% of hemophilic patients revealed previous infections due to hepatitis B virus (HBV) or hepatitis C virus (HCV); this rate was higher than in normal population.[6] HCV infection is frequently observed in patients with chronic liver disease coagulopathies.[7,8] The onset of clinical cirrhosis is estimated to occur 12-18 years from the start of the use of clotting factor concentrates.[9]

It is now accepted that the HCV-RNA load is higher in patients coinfected with HIV than in HIV negative individuals, while the relationship between HCV-RNA load and CD4+ lymphocyte count is still controversial.[2,5,10-12] Two studies on HCV/HIV coinfected hemophiliacs reported high HCV-RNA load and low CD4+ lymphocytes count[2,12] in patients with liver failure.

A single measurement of serum HIV-RNA has been reported as being of important prognostic value, and being strongly associated with rapid progression to AIDS and increased risk of mortality, regardless of treatment.[13,14] Because variability in the measurement of HIV-RNA levels may significantly affect their interpretation in clinical practice, repeated measures of HIV-RNA levels are now routinely made both in clinical trials and clinical practice.[15] To our knowledge, no study until now has reported the concomitant measurement of HCV-HIV RNA loads and CD4+ lymphocyte count in coinfected hemophiliacs.

After caring for a patient with coagulopathy, who was coinfected by HCV and HIV and who rapidly developed liver failure, we designed a cross-sectional study to measure HCV-RNA load, HIV-RNA load and CD4+ lymphocyte count in coinfected patients with severe coagulopathy and examined the relationship between these parameters and the liver failure.

## Design and Methods

In January 1996 we performed a cross-sectional study of 163 patients with severe coagulopathy attending the hematology Department of "La Sapienza" University in Rome. Severe coagulopathy was defined as by plasma levels of factor VIII:C, IX:C and VII:C below 2%. The patients who fulfilled the following criteria were evaluated: a) severe coagulopathy in patients who had received clotting factors concentrates which had not undergone virus-inactivation; b) HCV and HIV coinfection; c) absence of HBsAg; d) absence of interferon treatment.

Of the 163 initial patients, 39 patients (Group 1) fulfilled the entry criteria; there were 36 males and 3 females, 33 of them had hemophilia A, 3 hemophilia B and 3 factor VII:C deficiency. Of the remaining 124 patients with severe coagulopathy, 105 were $HCV^+$, $HIV^-$ and $HBsAg^-$; of this group, only 15 patients (male/female = 15/0, hemophilia A = 14, hemophilia B = 1), comparable for age and HCV exposure time, were selected as control group (Group 2).

Blood was collected in sterile tubes from patients at the entry to the study. Serum was separated within thirty minutes after collection and immediately stored at –70°C. HCV-RNA load, biochemical, and ultrasonographic parameters of all 54 patients enrolled in this study were performed at entry to the study. In all 39 coinfected patients the $CD4^+$ lymphocyte absolute count and HIV-RNA load were measured. All patients have been followed for thirty months.

### *Date of HCV infection*

The date of HCV infection was assumed to correspond to the date of first exposure to not virus inactivated clotting factor concentrates prepared from pooled donations.[4]

### *Date of HIV seroconversion*

For each individual, date of HIV seroconversion was calculated as the median value of the seroconversion interval between the last HIV negative test and the first HIV positive test under a Weibull seroincidence distribution, as described elsewhere.[16,17]

### *Definition of liver failure*

Liver failure was defined[4] as the contemporary evidence of at least three of the following parameters: albumin < 3.5 g/dL, prolonged prothrombin time, jaundice and ascites. The prothrombin time, expressed as a ratio versus the value from pooled normal plasma, was considered prolonged when the values were above the upper limit of the normal range (normal range as ratio = 0.84-1.18). Jaundice was defined as a bilirubin concentration higher than twice the upper limit of the normal range. Ascites was detected by ultrasonographic evaluation.

Liver biopsy in patients with severe coagulopathy may cause serious hemorrhagic complications in about 20% of patients.[9] In our Department, liver biopsy was not, therefore, performed in such patients, and chronic hepatitis C was evaluated by indirect parameters.[1]

### *Viral therapy and prophylaxis*

Thirty-four out of the 39 coinfected patients received antiretroviral monotherapy (zidovudine or didanosine or zalcitabine). No antiretroviral therapy was administered to the remaining five coinfected patients who had a $CD4^+$ lymphocyte count above 400/µL. Out of twenty patients with a $CD4^+$ lymphocyte count below 200/µL, 18 received *Pneumocystis carinii* prophylaxis with trimethoprim (800 mg) and sulphamethoxazole (160 mg) twice daily three times every week. The other two patients, who could not tolerate trimethoprim-sulphamethoxazole were treated with aerosol administered pentamidine (300 mg once a month).

From December 1996 to March 1997 all patients with a $CD4^+$ lymphocyte count below 200 µL received protease inhibitors as HIV viral therapy.

None of the coinfected patients received therapy or prophylaxis for mycobacterial or cytomegaloviral infections.

### *Biochemical evaluation*

All measurement were made using standard methods. Serum ferritin (range 10-190 ng/mL) levels were measured by Microparticle Enzyme Immunoassay (MEIA) (Abbott Diagnostic).

### *Virologic methods*

All frozen specimens were retrieved and immediately tested.

HBsAg, HBeAg, HBeAb, HBcAb and HBsAb tests were performed using standard techniques.

HCV positivity was detected by a second generation ELISA test (Ortho Diagnostics). The HCV-RNA and HIV-RNA viral loads were measured in a virology laboratory (Istituto Superiore di Sanità, Rome, Italy), member of the World Viral Quality Control (VQC). The HCV-RNA load was measured using the Amplicor HCV Monitor test (Roche Diagnostic System Inc.). Extraction, amplification and detection were performed according to the manufacturer's instructions, starting from 100 µL of serum. This test has a sensitivity of 1,000 copies HCV-RNA/mL.

HIV positivity was detected by the ELISA test and confirmed by a Western blot method. The HIV-RNA viral load measurement was performed by the NASBA QT system (Organon Teknika). This test has a sensitivity of 4,000 HIV-RNA/mL copies.

The stability of serum HCV-HIV RNA loads was tested twice/day on three consecutive days for randomly chosen samples.

### *Imaging methods*

Hepatic longitudinal diameter, longitudinal splenic diameter, portal vein diameter, and presence of ascites and collateral vessels were evaluated by ultrasound using an electrically focused 3.75 MHz sectorial probe (Toshiba SSH-140A). Duplex Doppler hemodynamic evaluation was performed in order to evaluate the average speed of portal flow and the spectrum characteristic of the flow in the suprahep-

atic vein. Esophageal varicosity was diagnosed by esophagogastroscopy (EGDS).

### *Statistical analysis*

Statistical analysis was performed using BMDP statistical software (Berkeley, Ca., USA). Mean values and standard deviations of all evaluated variables were calculated for both groups. The analysis of variance was performed between mean values of parameters in coinfected patients (Group 1) and in the control group (Group 2).

In the 39 coinfected patients, the non-parametric Mann-Whitney U test was used to measure the differences between the five patients with liver failure and the remaining without liver failure.

Pearson's *r* coefficient was calculated for correlation analysis.

## Results

Analyses of variance of biochemical, ultrasonographic and virological parameters in coinfected and not coinfected patients are reported in Table 1. The significant differences between HCV/HIV coinfected and $HCV^+/HIV^-$ patients were: HCV-RNA load ($p$ = 0.01), longitudinal splenic diameter ($p$ = 0.02) and portal vein diameter ($p$ = 0.04). Alanine aminotransferase, albumin, ferritin and longitudinal hepatic diameter were not different between the two groups of patients (Table 1). The HCV-RNA load was not correlated with ALT levels ($r$ = 0.21, $p$ = 0.1).

Of the 54 patients selected according to the study criteria all had serologic evidence of past HBV infection (HBsAb/HBcAb positivity).

In coinfected patients a significant inverse correlation was found between $CD4^+$ lymphocyte count and HIV-RNA load ($r$ = –0.37, $p$ = 0.01), while $CD4^+$ lymphocyte count did not correlate with HCV-RNA load ($r$ = –0.23, $p$ = 0.08).

The 39 HCV/HIV coinfected patients had a mean HIV-RNA load of 205,913±456,311 copies/mL (range 4,000-2,500,000) and a mean $CD4^+$ lymphocytes count of 206.5±171/µL (range 5-693).

Of the 39 coinfected patients five (12.8%) had liver failure at the time of entering the study. At that time, liver failure was not present either in the 15 patients of Group 2 selected for age and HCV exposure time, or in the remaining 90 $HCV^+/HIV^-$ patients. Age, HCV exposure time and HIV seroconversion data were not significantly different in the five coinfected patients with liver failure from those in the remaining 34 $HCV^+/HIV^+$ patients (Table 2).

In the 39 coinfected patients the Mann-Whitney U test showed a significantly higher HIV-RNA load ($p$ = 0.007) and lower $CD4^+$ lymphocyte count ($p$ = 0.03) in the five patients with liver failure than in the remaining 34 (Table 2). The HCV-RNA load was similarly high in coinfected patients with liver failure (770,200±996,426 copies/mL) and without (623,496±682,239 copies/mL) ($p$ = 1.0)(Table 2).

Hepatic and splenic longitudinal diameters were significantly increased in patients with liver failure ($p$ = 0.003 and 0.0008, respectively). The average speed of portal flow was significantly lower in the five patients with liver failure ($p$ = 0.01)(Table 2).

**Table 1. Analysis of variance between HCV/HIV coinfected patients and those only HCV positive (control group).**

| *Number of patients* | *$HCV^+/HIV^+$* *39* | *$HCV^+/HIV^-$* *15* | *p* |
|---|---|---|---|
| Age (years) | 34.7±12.4 | 32.1±13 | 0.51 |
| HCV exposure time (years) | 22.8±4.0 | 21.3±3.0 | 0.17 |
| HCV-RNA load (copies/mL) | 643,872±717,687 | 161,573±276,896 | 0.01 |
| Albumin (g/dL) | 4.3±0.5 | 4.1±0.8 | 0.19 |
| Ferritin (ng/mL) | 336±508 | 104±94 | 0.08 |
| Alanine aminotransferase (ALT)(< 40 IU/L) | 70±37 | 73±39 | 0.77 |
| Hepatic longitudinal diameter (mm) | 142±12 | 140±9 | 0.59 |
| Splenic longitudinal diameter (mm) | 134±22 | 119±16 | 0.02 |
| Portal vein diameter (mm) | 12.5±1.3 | 11.5±1.6 | 0.04 |
| Average speed of portal flow (cm/sec) | 17.5±3 | 18.4±1.7 | 0.20 |

*Mean values±standard deviations are reported.*

**Table 2. Mann-Whitney U test of HIV-RNA load, HCV-RNA load, $CD4^+$ lymphocyte count and ultrasonographic parameters between coinfected patients with liver failure and without.**

| *Number of patients* | *Liver failure* *5* | *No liver failure* *34* | *p* |
|---|---|---|---|
| Age (years) | 37.6±15.5 | 34.3±12 | 0.8 |
| HIV seroconversion date (year) | 1,983.6±1.12 | 1,983±0.57 | 0.20 |
| HCV exposure time (years) | 24.8±1.9 | 22.5±4.2 | 0.25 |
| HIV-RNA load (copies/mL) | 764,599±978,542 | 131,562±246,049 | 0.007 |
| HCV-RNA load (copies/mL) | 770,200±996,426 | 623,496±682,239 | 1.0 |
| $CD4^+$ lymphocytes count (n/µL) | 52.6±55.6 | 229.1±170.3 | 0.03 |
| Hepatic longitudinal diameter (mm) | 156±22 | 140±12 | 0.003 |
| Splenic longitudinal diameter (mm) | 170±18 | 129±17 | 0.0008 |
| Portal vein diameter (mm) | 13.3±0.4 | 12.4±1.6 | 0.24 |
| Average speed of portal flow (cm/sec) | 13.8±3.2 | 18.1±3 | 0.01 |

*Mean values±standard deviations are reported.*

Out of the 54 patients studied, six coinfected patients died; five of liver failure within the 9th month of follow-up and one in the 27th month due to non-Hodgkin's lymphoma.

## Discussion

The main finding of this cross-sectional study is that HIV infection influences HCV infection in patients with HCV/HIV coinfection and coagulopathy.

HCV-RNA load was significantly higher in coinfected patients than in $HCV^+/HIV^-$ patients, in agreement with data reported by others.[2,5,10-12,18,19] Telfer *et al*.[2] reported an increase of HCV-RNA among 29 $HIV^+$ hemophiliacs compared with that in 29 $HIV^-$ controls, however, among the HIV positive patients there was no correlation between HCV-RNA load and $CD4^+$ cell count. The lack of correlation between HCV-RNA load and $CD4^+$ cell count was in agreement with data reported by Sherman *et al.*[10] on 13 HIV seropositive and 30 HIV seronegative subjects. On the other hand, Eyster *et al.*[12] reported a higher HCV-RNA load in 17 $HIV^+$ hemophiliacs than in 17 $HIV^-$ hemophiliacs, with a correlation between HCV-RNA load and $CD4^+$ cell count. In agreement with Telfer[2] and Sherman,[10] we did not find any correlation between HCV-RNA load and $CD4^+$ lymphocyte count in 39 HCV/HIV coinfected patients with coagulopathy.

Of the 39 HCV/HIV coinfected patients, five (12.8%) had liver failure; by contrast none of the 105 $HCV^+/HIV^-$ had liver failure, which is consistent with data reported by Eyster,[1] Telfer[2] and Makris.[4]

The five patients with liver failure had a significantly high HIV-RNA load, low $CD4^+$ lymphocyte count and advanced liver disease as suggested by ultrasonographic evaluation. Ultrasonography is considered an accurate method for predicting the diagnosis of decompensated liver cirrhosis.[20] Recently, ultrasonographic liver surface nodularity and average speed of portal flow have been shown to be independently associated with the diagnosis of compensated liver cirrhosis.[21] The average speed of portal flow was significantly reduced in the five patients with liver failure reported in this study.

Potential confounders to the clinical association of worsening liver disease in our group of HCV/HIV coinfected patients could be concomitant or prior administration of hepatotoxic drugs, presence of other infections diseases that may affect the liver (e.g. *Mycobacterium avium*, *Cytomegalovirus*) and the genotype of the HCV strain.

That hepatotoxic drugs had a role in determining liver failure in our five patients who received zidovudine or didanosine, sulphamethoxazole and trimethoprim cannot be excluded because the patients who received antiretroviral and prophylactic therapy did not undergo histologic liver evaluation.

None of our coinfected patients with severe coagulopathy developed *Mycobacterium avium* complex disease or *Cytomegalovirus* infection.

It has been suggested that the genomic heterogeneity observed in HCV infection could have epidemiological, clinical and therapeutic implications.[22] Recently, it has been reported that liver damage in $HIV^+$ patients with chronic hepatitis C seems to be directly influenced by HCV genotype 1b.[23] Other authors, however, have found that HIV infection is responsible for an increase in HCV viremia, irrespective of HCV genotype.[24] Moreover, despite the fact that different hepatitis C virus genotypes have been hypothesized to have potentially different relative infectivity and pathogenicity in hemophiliacs, no evidence supporting these findings was found by Jarvis *et al.*[25]

Another important point to consider is the duration of the HCV infection. Several studies[26,27] have shown that HCV infection may induce a deleterious effect in case of concomitant HIV infection. Nevertheless, many years are needed to observe significant morbidity and mortality related to HCV infection. Mean estimated duration of HCV infection (> 20 years) was similar in the two groups (Table 1) of patients evaluated in this study and emphasizes the influence of HIV disease on HCV infection.

Chronic hepatitis C is considered an emergent problem in the management of HCV/HIV coinfected patients with coagulopathy both because of the risk of death[4] and because of the low therapeutic index of interferon treatment.[28,29] Recently, several studies[30-32] showed that in HCV/HIV coinfected patients, protease inhibitor antiretroviral therapy reduces HIV replication and increases $CD4^+$ lymphocyte count, even if it does not seem to reduce HCV-RNA load.

The absence of other cases of liver failure over 30 months of follow-up in the remaining coinfected patients with coagulopathy may support the hypothesis that therapy with protease inhibitors improves immune function in HCV/HIV coinfected patients with coagulopathy.

In conclusion, HCV-RNA load was higher in $HIV^+$ than in $HIV^-$ patients with coagulopathy. Liver failure was found in HCV/HIV coinfected coagulopathic patients with severe immunodepression, expressed either by low $CD4^+$ lymphocyte count or by high HIV-RNA load. A longitudinal study is essential in order to establish whether HIV disease influences the outcome of HCV infection.

***Contributions and Acknowledgments***

*FD, AC and GG were the principal investigators, designed the study and wrote the paper. MGM was involved in patients management. SV was involved in the evaluation of HIV-RNA load. UDC and MET performed statistical analysis. GP contributed by the evaluation of HCV-RNA load. VD was involved in the radiological and ultrasonographic evaluation. PM reviewed the manuscript.*

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### Disclosures

*Conflict of interest: none.*

*Redundant publications: <50%. Preliminary data from this study were presented at the XVI[th] Congress of the International Society on Thrombosis and Haemostasis, held in Florence, Italy, June 6-12, 1997, abstract n. 1849.*

### Manuscript processing

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## References


1. Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. J AIDS 1993; 12:602-10.
2. Telfer P, Sabin C, Devereux H, Scott F, Dusheiko G, Lee C. The progression of HCV-associated liver disease in a cohort of haenophilic patients. Br J Haematol 1994; 87:555-61.
3. Dragoni F, Mazzucconi MG, Cafolla A, Gentile G, Peraino M, Gonzalez M. Rapid liver failure related to chronic C hepatitis in an HIV positive hemophilic patients with severe immunodepression. Haematologica 1996; 81:335-8.
4. Makris M, Preston FE, Rosendaal FR, Underwood JCE, Rice KM, Triger DR. The natural history of chronic hepatitis C in haemophiliacs. Br J Haematol 1996; 94:746-52.
5. 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.
6. Brettler DB, Alter HJ, Dienstag J, Forsberg AD, Levine PH. Prevalence of hepatitis C virus antibody in a cohort of hemophilia patients. Blood 1990; 76:254-6.
7. Garson JA, Tuke PW, Makris M, et al. Demonstration of viraemia patterns in haemophiliacs treated with hepatitis-C-virus contaminated factor VIII concentrates. Lancet 1990; 336:1022-5.
8. Simmonds P, Zhang LQ, Watson HG, et al. Hepatitis C quantification and sequencing in blood products, haemophiliacs and drug users. Lancet 1990; 336: 1469-72.
9. Triger DR, Preston FE. Chronic liver disease in haemophiliacs. Br J Haematol 1990; 74:241-5.
10. Sherman KE, O'Brien J, Gutierrez AG, et al. Quantitative evaluation of hepatitis C virus RNA in patients with concurrent human immunodeficiency virus infections. J Clin Microbiol 1993; 31:2679-82.
11. Lau JYN, Davis GL, Kniffen J, et al. Significance of serum hepatitis C virus RNA levels in chronic hepatitis C. Lancet 1993; 341:1501-4.
12. Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ. Increasing hepatitis C virus RNA levels in haemophiliacs: Relationship to human immunodeficiency virus infection and liver disease. Blood 1994; 84:1020-3.
13. Mellors JW, Rinaldo CR, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science 1996; 272:1167-70.
14. O'Brien WA, Hartigan PM, Martin D, et al. Changes in plasma HIV-1 RNA and CD4 lymphocytes counts and the risk of progression to AIDS. Veterans Affairs Cooperative Study Group on AIDS. N Engl J Med 1996; 334:426-31.
15. Carpenter CCJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1997. Updated recommendations of the International AIDS Society-USA Panel. JAMA 1997; 277:1962-9.
16. Chiarotti F, Palombi M, Schinaia N, Ghirardini A, Bellocco R. Median time from seroconversion to AIDS in Italian HIV-positive haemophiliacs: Different parametric estimates. Stat Med 1994; 13:163-75.
17. Chiarotti F, Palombi M, Schinaia N, Ghirardini A, Prospero L. Effects of different parametric estimates of seronversion time on analysis of progression to AIDS among italian HIV-positive haemophiliacs. Stat Med 1992; 11:591-601.
18. 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.
19. 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.
20. Di Lelio L, Cestari C, Lomazzi A, Beretta L. Cirrhosis: diagnosis with sonographic study of liver surface. Radiology 1983; 172:389-92.
21. Gaiani S, Gramantieri L, Venturoli N, et al. What is the criterion for differentiating chronic hepatitis from compensated cirrhosis? A prospective study comparing ultrasonography and percutaneous liver biopsy. J Hepatol 1997; 27:979-85.
22. Bukh J, Miller R. Diagnostic and clinical implications of the different genotypes of hepatitis C virus. Hepatology 1994; 20:256-9.
23. Samaniego JG, Soriano V, Castilla J, et al. Influence of hepatitis C virus genotypes and HIV infection on histological severity of chronic hepatitis C. Am J Gastroenterol 1997; 92:1130-4.
24. Cribier B, Schmitt C, Rey D. HIV increases hepatitis C viraemia irrespective of the hepatitis C virus genotype. Res Virology 1997; 148:267-71.
25. Jarvis LM, Ludlam CA, Ellender JA, et al. Investigation of the relative infectivity and pathogenicity of different hepatitis C virus genotypes in haemophiliacs. Blood 1996; 87:3007-11.
26. Sherman KE, Freeman S, Harrison S, Andron L. Prevalence of antibody to hepatitis C virus in patients infected with the human immunodeficiency virus. J Infect Dis 1991; 163:414-5.
27. Bonacini M, Ding L, Govindarajan S. HIV+HCV coinfection: comparison with HCV infection. Hepatology 1994; 20:A333.
28. Lau JYN, Mikozami M, Ohno T, Diamond DA, Kniffen J, Davis GL. Discrepancy between biochemical and virological responses to interferon-alpha in chronic hepatitis C. Lancet 1993; 342:1208-9.
29. Hanley JP, Jarvis LM, Andrews J, et al. Interferon treatment for chronic hepatitis C infection in hemophiliacs: Influence of virus load, genotype and liver pathology on response. Blood 1996; 87:1704-9.
30. Vento S, Garofano T, Renzini C, Casali F, Ferraro T, Concia E. Enhancement of hepatitis C virus replication and liver damage in HIV-coinfected patients on antiretroviral combination therapy. AIDS 1998; 12:116-7.
31. Rutschmann OT, Negro F, Hirschel B, Hadengue A, Anwar D, Perrin LH. 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.
32. Rockstroh JK, Theisen A, Kaiser R, Sauerbruck T, Spengler U. Antiretroviral triple therapy decreases HIV viral load but does not alter hepatitis C virus (HCV) serum levels in HIV-HCV-co-infected haemophiliacs. AIDS 1998; 12:829-30.