



Liver fibrosis progression in HIV/hepatitis C virus coinfecting patients with normal aminotransferases levels

Progressão da fibrose hepática em portadores de coinfeção HIV/vírus da hepatite C com níveis de aminotransferases normais

Fábio Heleno de Lima Pace¹, Lincoln Eduardo Vieira de Castro Ferreira², Antonio Eduardo Benedito Silva³ and Maria Lucia Gomes Ferraz³

ABSTRACT

Introduction: Approximately 30% of hepatitis C virus (HCV) mono-infected patients present persistently normal alanine aminotransferase (ALT) levels. Most of these patients have a slow progression of liver fibrosis. Studies have demonstrated the rate of liver fibrosis progression in hepatitis C virus-human immunodeficiency virus (HCV-HIV) coinfecting patients is faster than in patients infected only by HCV. Few studies have evaluated the histological features of chronic hepatitis C in HIV-infected patients with normal ALT levels. **Methods:** HCV-HIV coinfecting patients (HCV-RNA and anti-HIV positive) with known time of HCV infection (intravenous drug users) were selected. Patients with hepatitis B surface antigen (HBsAg) positive or hepatitis C treatment before liver biopsy were excluded. Patients were considered to have a normal ALT level if they had at least 3 normal determinations in the previous 6 months prior to liver biopsy. All patients were submitted to liver biopsy and METAVIR scale was used. **Results:** Of 50 studied patients 40 (80%) were males. All patients were treated with antiretroviral therapy. The ALT levels were normal in 13 (26%) patients. HCV-HIV co-infected patients with normal ALT levels had presented means of the liver fibrosis stages (0.77 ± 0.44 versus 1.86 ± 1.38 ; $p < 0.001$) periportal inflammatory activity (0.62 ± 0.77 versus 2.24 ± 1.35 ; $p < 0.001$) and liver fibrosis progression rate (0.058 ± 0.043 fibrosis unit/year versus 0.118 ± 0.102 fibrosis unit/year) significantly lower as compared to those with elevated ALT. **Conclusions:** HCV-HIV coinfecting patients with persistently normal ALTs showed slower progression of liver fibrosis. In these patients the development of liver cirrhosis is improbable. **Keywords:** Liver cirrhosis. Hepatitis C. HIV. Aminotransferase.

RESUMO

Introdução: Aproximadamente, 30% dos portadores de hepatite crônica C apresentam níveis de aminotransferases persistentemente normais (APNL). A maioria destes pacientes tem lenta progressão da fibrose hepática. Em portadores de coinfeção VHC-HIV, estudos têm demonstrado que a progressão da fibrose hepática é mais rápida que a observada em indivíduos infectados somente pelo VHC. Há poucos estudos que verificaram as características histológicas da hepatite crônica C em pacientes coinfectados pelo HIV APNL. **Métodos:** Portadores de coinfeção VHC-HIV (HCV-RNA e anti-HIV positivos) com tempo de infecção pelo VHC conhecido (uso de drogas intravenosas) foram selecionados. Aqueles com *hepatitis B surface antigen* (HbsAg) positivo ou que tenham sido submetidos à terapia antiviral para hepatite C antes da biópsia hepática foram excluídos. Pacientes com pelo menos 3 determinações normais da ALT nos últimos 6 meses antes da biópsia hepática foram considerados como tendo APNL. Todos foram submetidos a biópsia hepática que foi classificada de acordo com a escala METAVIR. **Resultados:** Foram incluídos 50 pacientes, 40 (80%) homens. Todos receberam terapia antirretroviral. Os níveis de ALT foram persistentemente normais em 13 (26%) pacientes. Pacientes coinfectados com APNL apresentaram menor média dos estágios de fibrose hepática ($0,77 \pm 0,44$ versus $1,86 \pm 1,38$; $p < 0,001$), dos índices de atividade inflamatória periportal ($0,62 \pm 0,77$ versus $2,24 \pm 1,35$; $p < 0,001$) e progressão mais lenta da fibrose hepática ($0,058 \pm 0,043$ unidades de fibrose/ano versus $0,118 \pm 0,102$ unidades de fibrose/ano) quando comparados àqueles com aminotransferases elevadas. **Conclusões:** Portadores de coinfeção VHC-HIV com APNL apresentam progressão mais lenta da fibrose hepática. Nessas pacientes o desenvolvimento de cirrose hepática é improvável.

Palavras-chaves: Cirrose hepática. Hepatite C. HIV. Aminotransferases.

1. Departamento de Gastroenterologia, Centro de Referência em Hepatologia, Universidade Federal de Juiz de Fora, Juiz de Fora, MG. 2. Unidade de Endoscopia Digestiva, Universidade Federal de Juiz de Fora, Juiz de Fora, MG. 3. Seção de Hepatites, Divisão de Gastroenterologia, Universidade Federal de São Paulo, São Paulo, SP.

Address to: Dr. Fábio Heleno de Lima Pace. R. Professor Ivan Dias Raimundo 20, Spina Ville II, 36036-785 Juiz de Fora, MG, Brasil.

Phone/Fax: 55 32 4009-5302

e-mail: fpace@oi.com.br

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INTRODUCTION

Due to shared risk factors for transmission of coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) it is a very common event. It is estimated that around 30% of HIV-infected patients are coinfecting with HCV in the United States and Europe¹⁻⁷. The mode of HIV acquisition is directly associated with prevalence rates of HCV co-infection. Thus, the prevalence of HCV among men who have sex with men is approximately 10%, while 70-90% of the intravenous drug users (IDU) are HCV co-infected^{1,8,9}.

Liver disease caused by HCV is now the leading cause of morbidity and mortality among HIV-infected patients in the developed world where classic severe immunodeficiency opportunistic infections have considerably declined as a result of the widespread use of potent antiretroviral therapy¹⁰⁻¹⁵.

Several studies have demonstrated the deleterious HIV immunodeficiency action on the natural history of chronic hepatitis C. The rate of liver fibrosis progression in HCV-HIV coinfecting patients is about 1.5 to 2 times faster than in patients infected only by HCV¹⁶⁻²⁰. However, most of the studies were carried out during the pre-highly active antiretroviral therapy (HAART) era and only HCV-HIV coinfecting patients with elevated aminotransferases levels were included, which may have overestimated the severity of the HCV induced liver disease.

The real effect of HAART on the natural history of chronic hepatitis C in HIV infected patients is still unclear. Two studies reported that HCV-HIV coinfecting patients submitted to HAART based on the use of protease inhibitors presented slower liver fibrosis progression^{21,22}. Another study published by Qurish et al. found that HAART reduced liver related mortality in HCV-HIV coinfecting patients²³. On the other hand, Zylberberg et al described that the immunologic reconstitution after HAART

accelerated progression of chronic hepatitis C to more advanced liver fibrosis stages²⁴ and Antonello et al reported that coinfecting patients showed a higher aspartate aminotransferase to platelet ratio index (APRI), a noninvasive liver fibrosis marker, after six months of HAART when compared with hepatitis C mono-infected patients²⁵.

Approximately 30% of chronic hepatitis C carriers present persistently normal alanine aminotransferase (ALT) levels. Most of these patients show mild histological lesions and have slow liver fibrosis progression^{26,27}. Prospective studies and outcome modeling projections suggest that the risk of liver disease progression towards severe fibrosis/cirrhosis is minimal at 10-15 years in hepatitis C virus carriers with persistently normal ALT²⁸.

In the world, few studies have evaluated the behavior of chronic hepatitis C in HIV-infected patients with normal aminotransferases levels²⁹⁻³¹. In HCV-HIV coinfecting Brazilian patients, the prevalence of individuals with normal aminotransferases levels, the rate of liver fibrosis progression and their histological characteristics, remain to be studied.

METHODS

From June 2001 to June 2004, there were, HCV-HIV coinfecting patients followed in Federal University of São Paulo, Brazil, based on serum antibody detection with a third generation enzyme-linked immunosorbent assay. Serum HCV-RNA was detected by qualitative polymerase chain reaction (PCR-Amplicor; Roche Diagnostic Systems). Only patients with known HCV infection duration were selected. The HCV infection onset was considered as the first year of intravenous drugs usage, or transfusion. Exclusion criteria: presence of hepatitis B surface antigen (HBsAg) or hepatitis C treatment before liver biopsy. Patients were considered to have

normal ALT if they had at least 3 normal determinations (lower than the upper limit of normal) in the previous 6 months prior to liver biopsy were included in Group 1 (G1). Patients with altered aminotransferases levels were included in Group 2 (G2). All patients were submitted to liver biopsy independent of ALT levels. Using METAVIR classification, a single experienced pathologist performed the histological evaluation. The fibrosis progression rate (FPR) was defined as the ratio between the fibrosis stage and HCV infection duration (fibrosis units/year). To calculate the time required until the development of cirrhosis was divided 4 (F4 = cirrhosis) by the fibrosis progression rate in fibrosis units/year. Advanced liver fibrosis and intense inflammatory activity was considered when they are ≥ 2 .

Statistical analyses

Quantitative variables were expressed as average \pm standard deviation (SD) and were compared using the Student's *t*-test. Percentages were compared using χ^2 test and Fisher's exact test when appropriate. A difference was considered significant if the P-value was less than 0.05. The Statistical Package for the Social Sciences (SPSS) software package version 10 (SPSS Inc., Chicago, IL) was used.

Ethical considerations

The study was approved by the Research Ethics Committee of the São Paulo Hospital of the Federal University of São Paulo.

RESULTS

Seventy-nine patients with positive antibody anti-HCV and HCV infection with known duration were selected. Three of these were excluded by presenting the HBsAg, four due to the absence of HCV-RNA, and 22 patients for loss of the pursuing or refusing the

liver biopsy. Then, 50 patients were included. The average age at liver biopsy was 38 ± 6.6 years and 40 (80%) were males. The use of intravenous drugs was considered the virus acquisition mode in 43 (86%) patients. All patients were treated with antiretroviral therapy and 82% of them used HAART (Table 1). The cluster of differentiation (CD4) cell count was above 200 cells/mm³ in 84% of patients and the HIV viral load was less than 400 copies/mm³ in 48% of the sample (Table 2). The ALT levels were considered normal in 13 (26%) patients. Advanced liver fibrosis (fibrosis stage ≥ 2) and inflammatory activity ≥ 2 were identified in 36% and 54% of the sample, respectively (Table 3).

Regarding ALT levels, both of groups showed similar demographic characteristics and alcohol consumption (Table 1). In addition, the immunological parameters related to HIV infection and genotype distribution were not different between two groups (Table 2).

With respect to histological findings, the HCV-HIV co-infected patients with normal ALT levels had an average of the liver fibrosis stages (0.77 ± 0.44 versus 1.86 ± 1.38 ;

TABLE 1 - Comparative analysis of clinical characteristics between patients with normal and altered aminotransferases levels (n = 50).

Variables	All (n = 50)		Normal ALT (n = 13)		Altered ALT (n = 37)		P
	n	%	n	%	n	%	
Men	40	80.0	11	85.0	29	78.0	NS
Age at biopsy - years (mean \pm SD)	38.5 \pm 6.6		38 \pm 7.8		39 \pm 6.2		NS
Age at HCV infection - years (mean \pm SD)	21.5 \pm 7.9		22 \pm 8.4		21 \pm 7.8		NS
HCV infection duration - years (mean \pm SD)	17.1 \pm 5.5		16 \pm 5.5		17 \pm 5.5		NS
Alcohol consumption > 50g/day	25	50.0	6	46.0	19	51.0	NS
Drug intravenous user	43	86.0	10	77.0	33	89.0	NS
HAART	41	82.0	11	85.0	30	81.0	NS
PI use	23	46.0	6	46.0	17	46.0	NS

ALT: alanine aminotransferase; SD: standard deviation; HCV: hepatitis C virus; HAART: highly active anti-retroviral therapy; PI: protease inhibitor; NS: not significant.

TABLE 2 - Comparative analysis of biological parameters between patients with normal and altered aminotransferases levels (n = 50).

Variables	All (n = 50)		Normal ALT (n = 13)		Altered ALT (n = 37)		p
	n	%	n	%	n	%	
CD4 count - cells/mm ³ (mean \pm SD)	424.3 \pm 234.4		472 \pm 332		407 \pm 191		NS
HIV viral load - copies/mm ³ (mean \pm SD)	13.451 \pm 28.452		14.016 \pm 17.808		12.847 \pm 31.556		NS
CD4 count > 200cells/mm ³	42	84.0	11	85.0	31	84.0	NS
HIV viral load < 400/copies	24	48.0	5	38.0	19	51.0	NS
HCV genotype* non-1	28/43	65.0	10	77.0	18	48.0	0.11

ALT: alanine aminotransferase; CD4: cluster of differentiation; SD: standard deviation; HIV: human immunodeficiency virus; HCV: hepatitis C virus; *n=43; NS: not significant.

p<0.001) and periportal inflammatory activity (0.62±0.77 versus 2.24±1.35; p<0.001) significantly lower when compared to HCV-HIV coinfecting patients with altered aminotransferases levels. None of the patients with normal ALT levels had advanced liver fibrosis stages. Only two (15%) patients of group 1 had severe inflammatory activity. Furthermore, HCV-HIV co-infected patients with normal aminotransferases levels showed significantly lower liver fibrosis progression rates (0.058±0.043 fibrosis unit (FU)/year versus 0.118±0.102 FU/year) when compared to patients from group 2 (Table 3). The interval between HCV infection and development of liver cirrhosis (F4), assuming that the fibrosis progression rate is linear, it was 69 (F4/0.058) and 34 years (F4/0.118) for groups 1 e 2, respectively (Figure 1).

DISCUSSION

In healthy patients the normal range for serum ALT level was set in the 1955 by Karmen³² and has changed little since then. Current upper limit of normality (ULN) were set, on average, from 30 to 50U/L. This was recently challenged by a research group, who claimed that the true normal values are significantly lower. Prati et al suggested that the updated upper limit of normality of alanine aminotransferase should be 30U/L for males and 19U/L for females in subjects with the lowest risk for liver disease³³.

In chronic hepatitis C patients the definition of persistently normal ALT activity (PNALT) no has consensus. Guidelines from the American Association for the Study of Liver Disease suggest that at least two ALT measurements within the normal range taken over at least 6 months can define those with PNALT³⁴. Fonquernie et al. considered PNALT coinfecting patients with normal ALT levels documented by repeated testing (at least three values per year) over a 3-year period²⁹. A French study by Bani-Sadr et al, coinfecting patients with persistently normal ALT levels were defined as those having three consecutive persistently normal ALT levels over a 6-month period³⁰ the same criteria adopted in this study.

Although chronic HCV infection is associated with elevation of ALT activity in most patients, approximately 25% presented serum ALT activity that is persistently within the normal range³⁵. Fonquernie et al. reported among 155 HCV-HIV coinfecting patients, 39 (28.5%) had persistently normal ALT levels²⁹. In study involving 381 HCV-HIV coinfecting patients, Bani-Sadr et al. identified 36 (9.4%) subjects with persistently normal ALT values³⁰. Sanchez-Conde et al. reported 24/256 (9.4%) HIV-HCV coinfecting patients with persistently normal ALT levels³¹. In the present study, we found 13/50 (26%) coinfecting patients on HAART with persistently normal aminotransferases levels. The variable criteria of PNALT used among several studies may explain the different prevalence rates observed.

In chronic hepatitis C, comparisons between normal and elevated ALT patients have not identified clear differences that could be used as ALT level predictive factors. In this study, there was a tendency to genotype non-1 in patients with altered aminotransferases levels (9% versus 44%; p=0.06). In the Sanchez-Conde study, patients infected with HCV genotype 3 were significantly more common

TABLE 3 - Comparative analysis of histological findings between patients with normal and altered aminotransferases levels (n = 50).

Variables	Normal ALT (n=13)		Elevated ALT (n=37)		P
	n	%	n	%	
Liver fibrosis stage (mean ± SD)	0.77±0.44		1.86±1.38		< 0.0001
Inflammatory activity (mean ± SD)	0.62±0.77		2.24±1.35		< 0.0001
FPR (mean ± SD)	0.058±0.043		0.118±0.102		0.006
Fibrosis stage ≥ 2 (n/%)	0	0.0	18	49.0	0.002
Inflammatory activity ≥ 2 (n/%)	2	15.0	25	68.0	< 0.0001

ALT: alanine aminotransferase; SD: standard deviation; FPR: fibrosis progression rate in units fibrosis/year.

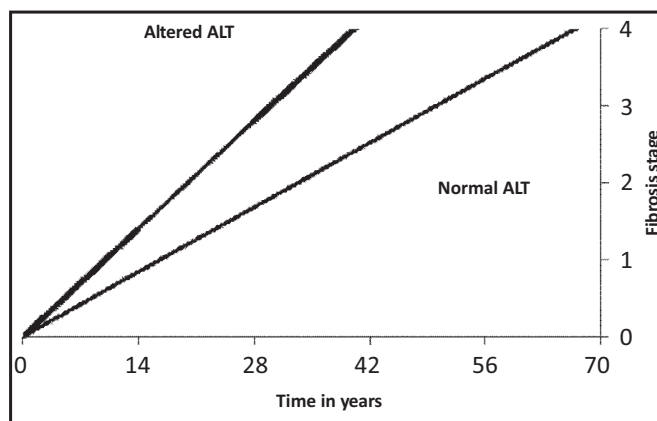


FIGURE 1 - Estimated time to the development of liver cirrhosis according to the ALT levels (n = 50).

ALT: alanine aminotransferase.

between patients with altered ALT levels than in patients with persistently normal ALT levels³¹. In the Bani-Sadr study, a lower mean METAVIR inflammation score, the absence of steatosis and HCV genotype 4 were associated with persistently normal ALT levels³⁰. In the Fonquernie study, three factors associated with persistently normal ALT levels were identified, namely: HBsAg negativity, HCV genotype 4 and female sex²⁹.

The natural history of chronic hepatitis C is variable. Since most patients with HCV-related chronic hepatitis do not develop cirrhosis, it is logical to infer that host-related and virus-related factors must play a role in the progression to cirrhosis. Liver disease progression takes place over several decades, and is accelerated in the presence of cofactors such as alcohol consumption, insulin resistance, steatosis, older age of acquisition and HIV coinfection. Definition of histological features and liver disease progression in individuals with HCV and normal ALT is complicated because the absence of a gold standard definition for PNALT. Nevertheless, it is generally accepted that individuals with PNALT have milder liver histology when compared to patients with elevated aminotransferases levels^{36,37}.

Most studies have shown that in HCV-HIV coinfecting patients liver fibrosis progression is faster than in HCV mono-infected patients¹⁶⁻²⁰. There are few studies that analyze liver histology in HIV-HCV coinfecting patients with PNALT. In this study, individuals with normal aminotransferase levels showed mild histological lesions and slower liver fibrosis progression. In the Bani-Sadr study, none of the 36 patients with PNALT had cirrhosis³⁰. In coinfecting patients with normal aminotransferases levels Fonquernie et al demonstrated a significantly lower fibrosis score and fibrosis progression rate²⁹. In this study, factors known to be related to the progression of chronic hepatitis C in mono-infected patients such gender, alcohol consumption and age at time of infection were similar in both groups.

The variables related to cirrhosis development in coinfecting patients in accordance with Benhamou study were similar too¹⁷. The slower progression of liver fibrosis in coinfecting patients with persistently normal ALT levels could be related, in part, to a lower frequency of steatosis in accordance with the Bani-Sadr study³⁰. In the present study, this histological feature was not analyzed. In this study only two patients (15%) in PNALT group showed significant inflammatory activity which may in part at least explain the slower liver fibrosis progression rate in these patients. Potential limitations that could affect this study's results is that the number of PNALT patients was not high and the absence of a uniform definition for PNALT makes comparisons across different studies difficult.

In conclusion, this study could demonstrate that HCV-HIV coinfecting patients with persistently normal aminotransferases exposed to antiretroviral therapy would show mild histological lesions. In these patients liver cirrhosis development is improbable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

- Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet* 2000; 356:1800-1805.
- Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. *JAMA* 2002; 288:199-206.
- Brau N, Bini EJ, Shahidi A, Aytaman A, Xiao P, Stancic S, et al. Prevalence of hepatitis C and coinfection with HIV among United States veterans in the New York City metropolitan area. *Am J Gastroenterol* 2002; 97:2071-2078.
- Sherman KE, Rouster SD, Chung RT, Rajcic N. Hepatitis C Virus prevalence among patients infected with human immunodeficiency virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis* 2002; 34:831-837.
- Quaranta JF, Delaney SR, Alleman S, Cassuto JP, Dellamonica P, Allain JP. Prevalence of antibody to hepatitis C virus (HCV) in HIV-1-infected patients. *J Med Virol* 1994; 42:29-32.
- 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; 29:150-154.
- Ockenga J, Tillmann HL, Trautwein C, Stoll M, Manns MP, Schmidt RE. Hepatitis B and C in HIV-infected patients. Prevalence and prognostic value. *J Hepatol* 1997; 27:18-24.
- Saillour F, Dabis F, Dupon M, Lacoste D, Trimoulet P, Rispal P, et al. Prevalence and determinants of antibodies to hepatitis C virus and markers for hepatitis B virus infection in patients with HIV infection in Aquitaine. *BMJ* 1996; 313:461-464.
- Mendel I, Clotteau L, Lambert S, Buffet-Janvresse C. Hepatitis C virus infection in HIV-positive population in Normandy: antibodies, HCV RNA and genotype prevalence. *J Med Virol* 1995; 47:231-236.
- Palella Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; 338:853-860.
- Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001; 32:492-497.
- Cacoub P, Geffray L, Rosenthal E, Perronne C, Veysier P, Raguin G. Mortality among human immunodeficiency virus-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; 32:1207-1214.
- Rosenthal E, Poiree M, Pradier C, Perronne C, Salmon-Ceron D, Geffray L, et al. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS* 2003; 17:1803-1809.
- Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet* 1998; 352:1725-1730.
- Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 2003; 362:22-29.
- Sanchez-Quijano A, Andreu J, Gavilan F, Luque F, Abad MA, Soto B, 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; 14:949-953.
- Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group. *Hepatology* 1999; 30:1054-1058.
- Soto B, Sanchez-Quijano A, Rodrigo L, del Olmo JA, Garcia-Bengochea M, Hernandez-Quero J, 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.
- Mohsen AH, Easterbrook PJ, Taylor C, Portmann B, Kulasegaram R, Murad S, et al. Impact of human immunodeficiency virus (HIV) infection on the progression of liver fibrosis in hepatitis C virus infected patients. *Gut* 2003; 52:1035-1040.
- Martin-Carbonero L, Benhamou Y, Puoti M, Berenguer J, Mallolas J, Quereda C, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. *Clin Infect Dis* 2004; 38:128-133.
- Benhamou Y, Di Martino V, Bochet M, Colombet G, Thibault V, Liou A, et al. Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-coinfecting patients: impact of protease inhibitor therapy. *Hepatology* 2001; 34: 283-287.
- Macias J, Castellano V, Merchante N, Palacios RB, Mira JA, Saez C, et al. Effect of antiretroviral drugs on liver fibrosis in HIV-infected patients with chronic hepatitis C: harmful impact of nevirapine. *AIDS* 2004; 18 :767-774.
- Qurish N, Kreuzberg C, Luchters G, Effenberger W, Kupfer B, Sauerbruch T, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet* 2003; 362:1708-1713.
- Zylberberg H, Pialoux G, Carnot F, Landau A, Brechot C, Pol S. Rapidly evolving hepatitis C virus-related cirrhosis in a human immunodeficiency virus-infected patient receiving triple antiretroviral therapy. *Clin Infect Dis* 1998; 27:1255-1258.
- Antonello VS, Tovo CV, Kliemann DA, Santos BR, Zaltron VF. Evaluation of APRI score in liver disease following the introduction of antiretroviral therapy in HIV and HCV coinfecting versus HIV mono-infected patients. *Rev Soc Bras Med Trop* 2010; 43:678-681.
- Alberti A, Noventa F, Benvegno L, Boccato S, Gatta A. Prevalence of liver disease in a population of asymptomatic persons with hepatitis C virus infection. *Ann Intern Med* 2002; 137:961-964.
- Pradat P, Alberti A, Poynard T, Esteban JI, Weiland O, Marcellin P, et al. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. *Hepatology* 2002; 36:973-977.
- Alberti A, Benvegno L, Boccato S, Ferrari A, Sebastiani G. Natural history of initially mild chronic hepatitis C. *Dig Liver Dis* 2004; 36:646-654.
- Fonquernie L, Serfaty L, Charrois A, Wendum D, Lefebvre B, Girard PM, et al. Significance of hepatitis C virus coinfection with persistently normal alanine aminotransferase levels in HIV-1-infected patients. *HIV Med* 2004; 5:385-390.
- Bani-Sadr F, Barange K, Daoud F, Jacomet C, Bicart-See A, Rosenthal E, et al. Persistently normal alanine aminotransferase levels in HIV/HCV-coinfecting patients: the role of steatosis. *HIV Med* 2009; 10:417-421.
- Sanchez-Conde M, Berenguer J, Miralles P, Alvarez F, Carlos Lopez J, Cosin J, et al. Liver biopsy findings for HIV-infected patients with chronic hepatitis C and persistently normal levels of alanine aminotransferase. *Clin Infect Dis* 2006; 43:640-644.
- Karmen A, Wroblewski F, Ladue JS. Transaminase activity in human blood. *J Clin Invest* 1955; 34:126-131.
- Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002; 137:1-10.
- Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004; 39:1147-1171.
- Zeuzem S, Alberti A, Rosenberg W, Marcellin P, Diago M, Negro F, et al. Review article: management of patients with chronic hepatitis C virus infection and "normal" alanine aminotransferase activity. *Aliment Pharmacol Ther* 2006; 24:1133-1149.
- Shiffman ML, Diago M, Tran A, Pockros P, Reindollar R, Prati D, et al. Chronic hepatitis C in patients with persistently normal alanine transaminase levels. *Clin Gastroenterol Hepatol* 2006; 4:645-652.
- Persico M, Perrotta S, Persico E, Terracciano L, Folgori A, Ruggeri L, et al. Hepatitis C virus carriers with persistently normal ALT levels: biological peculiarities and update of the natural history of liver disease at 10 years. *J Viral Hepat* 2006; 13:290-296.