

Natural history and predictors of severity of chronic hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection

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Co-infection by the hepatitis C virus (HCV) is observed in up to 30% of HIV-infected individuals. In studies conducted in the 'pre-HAART era', the late consequences of HCV-related chronic liver disease were overshadowed by extra-hepatic causes of deaths, related to severe immune deficiency, and the impact of HCV infection on mortality of HIV-infected patients was low. While the development of HAART has resulted in a significant decrease in morbidity and mortality amongst HIV-infected patients, this clear benefit allowed the expression of liver-related complications associated with HCV chronic infection. The impact of HCV on HIV remains debated but HIV infection significantly modifies the natural history of HCV infection. HIV infection increases levels of HCV viraemia by 2- to 8-fold, resulting in a significant decrease in spontaneous recovery of acute hepatitis. HIV co-infection also worsens the histological course of HCV infection by increasing and accelerating the risk of cirrhosis or leading to rare but lethal fibrosing cholestatic hepatitis. Liver disease is now one of the leading causes of morbidity and mortality in co-infected patients, even if HAART and especially protease inhibitors, may decrease the severity of the liver disease and the liver-related mortality. Several non-exclusive pathogenic processes explain the increasing rate of liver complications associated with HCV-related liver disease.

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Keywords: hepatitis C; HIV; co-infection; interaction

1. Introduction

Co-infections by hepatotropic viruses and HIV are frequent given the shared (sexual, mother-to-child and parenteral) routes of transmission. We shall mainly focus on the natural history of HCV-related disease in HIV-infected patients before the introduction of highly active antiretroviral therapies (HAART) [1–3] and in patients under HAART emphasising causes of death and predictors and co-factors of disease severity [4]. In studies conducted in the 'AIDS era' (pre-HAART), the late consequences of HCV-related chronic liver disease were overshadowed by extra-hepatic causes of deaths, related to severe immune deficiency, namely opportunistic infections, lymphomas or

wasting syndrome [5–7] and the impact of HCV infection on mortality of HIV-infected patients was low [4].

The development of HAART (regimens composed of nucleoside reverse transcriptase inhibitors [NRTIs], protease inhibitors [PIs] and/or non-nucleoside reverse transcriptase inhibitors [NNRTIs]) resulted in a significant decrease in morbidity and mortality amongst HIV-infected patients [8–10]; this benefit allowed the expression of liver-related complications associated with HCV chronic infection which is mainly acquired before HIV infection, at least in haemophiliacs and intravenous drug users (IVDUs). Liver disease is nowadays one of the leading causes of morbidity and mortality in co-infected patients [11–14]. Several non-exclusive pathogenic processes that include drug-related hepatotoxicities, chronic HCV infection, other liver diseases such as steatosis or non-alcoholic steatohepatitis (NASH) and other liver diseases that are common in the setting of alcohol or drug abuse explain the increasing

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rate of liver complications associated with HCV-related liver disease [11]. They account for around 10–15% of morbidity and mortality in HIV–HCV co-infected patients [11] with a rise paralleling that observed in the general population [15,16], even if it has been suggested that HAART and especially protease inhibitors may decrease the severity of the liver disease [17] and the liver-related mortality [18].

2. Pathogenic reciprocal interactions between HIV and HCV before HAART

2.1. Prevalence of HCV/HIV co-infection

Anti-HCV antibodies are frequently detected in HIV-infected patients (around 30% by third generation ELISA assays), especially in haemophiliacs and IVDUs (around 70–90%) and are usually associated with active infection as assessed by detectable HCV viraemia [1–3,19]. Given the good sensitivity and specificity of the third-generation tests, the risk of underestimation by delayed anti-HCV seroconversions [20] or seroreversions [21] is now low.

2.2. Reciprocal consequences of the HIV/HCV co-infection

Despite most early studies failing to show a change of the natural history of HIV infection associated with HCV infection [22–24] later studies have indicated that genotype 1b HCV may worsen the spontaneous evolution of HIV to both AIDS and death in haemophiliacs as well as in drug users [25–27]. Moreover, HCV infection (and active intravenous drug use) has been suggested as an important factor in the morbidity and mortality among HIV-1-infected patients, possibly through impaired CD4-cell recovery in HCV seropositive patients receiving potent antiretroviral therapy [28]. Several non-exclusive mechanisms potentially explain how HCV may act as co-factor of HIV disease progression including unspecific immune stimulation enhancing HIV replication, CD4 T-cell depletion reflecting infection of immune cells by HCV or HAART discontinuation favoured by the underlying liver disease (see below).

HIV infection significantly modifies the natural history of HCV infection [1–3]. HIV infection increases levels of HCV viraemia [29–32] and HIV seroconversion increase HCV-RNA titres [33]. This 2- to 8-fold increase results in a significantly lower rate of spontaneous recovery of acute hepatitis from 0% (personal data) to 25% [34], an increased risk of mother-to-child or sexual transmission (from a mean of 6–20% and from 0 to 3%, respectively) [35,36]. HIV co-infection worsens the histological course of HCV infection by increasing and accelerating the risk of cirrhosis [37–42] or leading to rare but lethal fibrosing cholestatic hepatitis which is clearly related to direct cytotoxicity of HCV with high viraemia leading to accumulation of viral proteins in the endoplasmic reticulum and hepatocyte death [43].

Indeed, the rate of cirrhosis is 2- to 5-fold increased in HIV/HCV co-infected patients as compared to HCV-infected patients and the mean time elapsed between contamination and cirrhosis is significantly reduced [44]. This increased rate of cirrhosis and shorter evolution is explained by a significantly increased yearly progression of the fibrosis score in co-infected subjects [45], which depends on the CD4-cell count (<200 cells/ml). The influence of chronic alcohol consumption or HBV-HCV mixed infections remains debated (38,45).

The more severe liver disease observed in all the situations of immune deficiency may reflect, at least partially, a deleterious impact of increased viraemia.

3. Pathogenic reciprocal interactions between HIV and HCV in the HAART era

HCV infection appears to have a limited impact on response to antiretroviral therapy: the early delayed CD4 count recovery [28] is not sustained and is not associated with increased HIV disease progression [46].

High-level expression of HCV proteins may lead to cellular injury: the expression of HCV proteins in cell lines diminishes the proliferative capacity of cells [47]. By contrast with the direct HBV cytotoxicity which can be controlled by the use of nucleoside or nucleotide RTIs (lamivudine, emtricitabine, adefovir dipivoxyl or tenofovir) [48–50], antiretroviral drugs do not control HCV infection. Only anecdotal cases of the disappearance of detectable HCV RNA have been described in patients receiving HAART (especially ritonavir) [51]. Significant restoration of CD4 and CD8 cell counts rarely decreases serum HCV load and there is no relevant decrease, as compared to baseline values, in HCV RNA loads after 3, 6, or 9 months of HAART in HCV/HIV co-infected individuals [52,53]. These data suggest that HAART does not clearly decrease the incidence of HCV-related liver disease associated with HCV replication.

A marked decrease in the CD4 cell count may modify the re-partition of HCV quasi-species with a putative risk of selection of HCV quasi-species with increased pathogenicity [54]. At the opposite and given the immune-mediated pathogeny of HCV, the enhancement of immunity could be deleterious (hepatitis of immune restoration) as reported after withdrawal from chemotherapy in HCV-infected people [55]. The number of liver CD8 T lymphocytes directed against specific HCV antigens correlate with disease activity and it is known that HAART restores the numbers of both CD4 and CD8 cells [56,57]. Since the introduction of HAART, several cases of liver deterioration paralleling the immune restoration in HCV/HIV co-infected patients have been reported [58,59]. This phenomenon has been previously reported in cases of HBV infection, regardless of the cause of immune suppression [60], and has been suggested in cases of HCV infection [61].

Physicians should be aware and a sensitive liver follow-up in HCV/HIV co-infected patients taking HAART is needed and calls into question the respective temporal sequence of anti-HCV and anti-HIV therapies. On the contrary, it has been suggested that HAART and especially PIs may decrease the severity of the liver disease: chronic use of PIs and maintenance of high CD4 count could have a beneficial impact on liver fibrosis progression in HIV/HCV co-infected patients [17].

4. Predictors and co-factors of disease severity

4.1. Drug-related hepatotoxicity

Each component of HAART may result in drug-related hepatotoxicity [13,41]. All classes of antiretroviral drugs have been associated with liver enzyme abnormalities; the prevalence of these cases is not well defined and varies according to the studies and their methodology. Early diagnosis of drug-associated hepatic events is difficult since most HIV-infected patients do not fulfil the semiological and chronological signs that allow a clear diagnosis of drug-related hepatotoxicity [62–65], except for the typical but rare cases of idiosyncratic hepatitis [66]. Patients are treated with polypharmacy, they may use alcohol or drugs and HBV or HCV co-infection occurs in up to 30% of cases. Hepatotoxicity related to the use of NRTIs, especially zidovudine, stavudine and didanosine [67], correspond to exceptional cases of severe microsteatosis with lactic acidosis [68]. PI-related hepatitis is observed in 2–8.5% of PI-treated patients [69–71], with an increased risk in patients co-infected with HBV or HCV [71,72]. Liver toxicity, including fulminant hepatitis, has been associated with NNRTIs and pre-existing liver disease increases the relative risk [66,73,74].

In most cases of drug-related hepatitis, apart from fulminant presentations, liver enzyme abnormalities resolved after discontinuation of the drug and did not relapse, for example, after changing the PI [75]. We speculate that drug-related hepatitis may be involved in the deteriorating liver histology, including mechanisms associated with drug-related NASH [76].

4.2. Other causes of liver damage in HIV/HCV co-infected patients

Paralleling HAART-related hepatotoxicity and HCV-chronic hepatitis, HIV-infected patients may have other risk factors for liver enzyme elevations. These mainly include alcohol consumption, drug or other medications abuse and abnormal metabolic syndromes. The impact of these three last co-factors of liver deterioration has not been clearly analyzed in co-infected patients. The deleterious consequences of alcohol in HCV-mono-infected patients include: increase in levels of HCV RNA [77], which resolve with

alcohol withdrawal [78] and this is usually achieved [79]; and increase in fibrosis progression [45,80]. In any case, in co-infected as well as in mono-infected patients, alcohol withdrawal appears necessary to limit its detrimental impact and also to improve the immune situation [81]. Chronic alcohol consumption is observed in 30% of HIV-infected patients (at least ex-drug abusers) [40,45] and may induce alcoholic hepatitis leading to liver deterioration [76]. Interestingly, alcohol, may per se enhance drug-related toxicity [82,83].

Drugs, especially cocaine and methamphetamine, have their own hepatic effects and these are sometimes severe (e.g. fulminant hepatitis with renal failure and rhabdomyolysis) [84,85].

Finally, abnormal metabolic syndromes may participate in liver deterioration of co-infected patients and include NASH in relation to abnormal metabolic syndromes (such as diabetes and dyslipidaemia) and to HAART or HAART-related metabolic syndromes [86,87]. The potential involvement of NASH in liver biochemical abnormalities and pathological deterioration is suggested by the significantly higher frequency of steatosis, Mallory bodies and neutrophils infiltrates in HIV-positive than negative patients [76]. This may be due to the effects of the antiretroviral therapy on the mitochondria [65,88,89], triggering lipid peroxidation and the release of pro-inflammatory cytokines, which favour fibrosis and apoptosis. As in immunocompetent patients, steatosis may be an independent factor associated with fibrosis progression, especially those infected with genotype 3 HCV or in overweight patients [90,91].

All of these co-factors can be partially controlled by effective and less toxic antiretroviral therapies and by medical counselling including advice on reducing alcohol consumption.

5. Morbidity and mortality

The decline of HIV-related mortality after the widespread use of HAART paralleled the emergence of HCV-related liver disease as an important cause of mortality among co-infected patients—estimates range from 10 to 45% [92–94]. In a nationwide cohort of HIV-infected patients followed-up from 1995 to 2003, mortality due to end-stage liver disease (ESLD) progressively increased over time and became a leading cause of mortality [4,13,95]. Among the 20,940 HIV-infected patients followed in 2003, 215 deaths occurred (mortality rate of 1%) [95]; causes of death were AIDS, ESLD and other in 46.9, 12.6 and 40.4%, respectively. Between 1995 and 2001, although overall mortality significantly decreased from 8 to 1%, the proportion of deaths attributable to cirrhosis and/or hepatocellular carcinoma (HCC) increased from 1.5 to 14.3% [4,13], while from 2001 to 2003 both overall mortality and death due to ESLD (12.6% in 2003) were stable [95]. Among the patients who died from ESLD,

the percentage of patients with HCV infection was higher in 2003 (92.0%) than in 1995 (57.1%); HCC, as a cause of death, increased between 1995 and 2001 from 4.7 to 25% and decreased in 2003 (14.8%). In 2003, mortality attributable to ESLD seems to be steady which suggests a stabilization or a slowing down which may correspond either to a temporary trend or a sustained evolution. Finally, in 2003, ESLD-related death represented 24% of all non-AIDS-related deaths and constituted the most frequent non-AIDS-related cause of death in the HIV-positive population [95]. These data confirm results obtained from other French or European studies showing the primary and increasing importance of liver disease as a cause of mortality in the global HIV-population [96–100]. Several factors may explain the progressive increase of mortality due to ESLD observed since the introduction of HAART: prolonged longevity attributable to HAART, increased prevalence of alcohol use [13], or potential hepatotoxicity of HAART. In 2003, these may be counterbalanced by the favourable effect of hepatitis C treatment [101–104]. The role of HAART in liver disease progression and in overall mortality of HCV–HIV co-infected patients is still debated. HAART may be responsible for hepatotoxicity [13,41]. In contrast, other studies have suggested that the use of protease inhibitors may be protective with respect to the progression of HCV-related liver disease [17] and that HAART reduced long-term liver-related mortality, in addition to improved overall survival [18,105].

6. Conclusion

If the effect of HCV on HIV disease progression remains unclear, it is clear that HIV infection worsens the course of HCV infection. The development of HAART has resulted in a significant decrease in AIDS-related morbidity and mortality amongst HIV-infected patients allowing the expression of liver-related complications associated with the HCV chronic infection which is nowadays one of the leading causes of morbidity and mortality in co-infected

patients. The prolonged longevity attributable to HAART, and the increased prevalence of alcohol use and NASH may explain this progressive increase of mortality due to end stage liver disease. The favourable effect of hepatitis C treatment (combination of pegylated interferon and ribavirin) in this population may slow the progression of morbidity and mortality due to ESLD in the near future (Fig. 1).

References

- [1] Zylberberg H, Pol S. Reciprocal interactions between human immunodeficiency virus and hepatitis C virus infections. *Clin Infect Dis* 1996;23:1117–1125.
- [2] Soriano V, Rodriguez-Rosado R, Garcia-Samaniego J. Management of chronic hepatitis C in HIV-infected patients. *AIDS* 1999;13: 539–546.
- [3] Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected person. *Ann Intern Med* 2003;138:197–207.
- [4] Cacoub P, Geffray L, Rosenthal E, Perronne C, Veyssier P, Raguin G, et al. Mortality among human immunodeficiency virus-infected patients with cirrhosis or hepatocellular carcinoma due to hepatitis C virus in French Departments Internal Medicine/Infectious Diseases, in 1995 and 1997. *Clin Infect Dis* 2001;32:1207–1214.
- [5] Lebovics E, Dworkin BM, Heier SK, Rosenthal WS. The hepatobiliary manifestations of human immunodeficiency virus infection. *Am J Gastroenterol* 1988;83:1–7.
- [6] Lefkowitz JH. Pathology of AIDS-related liver disease. *Dig Dis* 1994;12:321–330.
- [7] Cappell MS. Hepatobiliary manifestations of the acquired immune deficiency syndrome. *Am J Gastroenterol* 1991;86:1–15.
- [8] Centers for disease control and prevention, update. Trends in AIDS incidence. *Morb Mortal Wkly Rep* 1997;46:165–73.
- [9] Lipsky James J. Antiretroviral drugs for AIDS. *Lancet* 1996;348: 800–803.
- [10] Pallela Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten G, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient study investigators. *N Engl J Med* 1998;338:853–860.
- [11] Soriano V, Garcia-Samaniego J, Valencia E, Rodriguez-Rosado R, Munoz F, Gonzalez-Lahoz J. Impact of chronic viral liver disease due to hepatitis viruses as cause of hospital admission and death in HIV-infected drug users. *Eur J Epidemiol* 1999;15:1–4.
- [12] 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.
- [13] Rosenthal E, Poirée M, Pradier C, Perronne C, Salmon-Céron D, Geffray L, et al. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (mortavic 2001 study). *Acq Immun Def Son* 2003;17:1803–1809.
- [14] Monga HK, Rodriguez-Barradas MC, Breaux K, Khattak K, Troisi CD, Velez M, et al. Hepatitis C virus infection-related morbidity and mortality among patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001;33:240–247.
- [15] Darby SC, Ewart DW, Giangrande PLF, Spooner RJD, Rizza CR, Dusheiko GM, et al. For the UK haemophilia centre directors' organisation. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. *Lancet* 1997;350:1425–1431.
- [16] El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999;340:745–750.

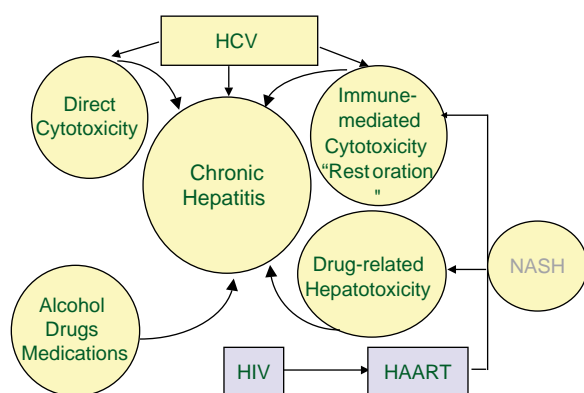


Fig. 1. Intrication of putative liver lesions in HIV–HCV co-infection. [This figure appears in colour on the web.]

- [17] 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-co-infected patients: impact of protease inhibitor therapy. *Hepatology* 2001;34:283–287.
- [18] Qurishi 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 infection. *Lancet* 2003;362:1708–1713.
- [19] Denis F, Adjide CC, Rogez S, Delpeyroux C, Rogez JP, Weinbreck P. Seroprevalence of HBV, HCV and HDV markers in 500 patients infected with the human immunodeficiency virus. *Pathol Biol* 1997;45:701–708.
- [20] Marcellin P, Martinot-Peignou M, Elias A, Branger M, Courtois F, Level R, et al. Hepatitis C virus (HCV) viraemia in human immunodeficiency virus-seronegative and seropositive patients with indeterminate HCV recombinant immunoblot assay. *J Infect Dis* 1994;170:433–435.
- [21] Chamot E, Hirschel B, Wintsh J, Robert CF, Gabriel V, Deglon JJ, et al. Loss of antibodies against hepatitis C virus in HIV-seropositive intravenous drug users. *AIDS* 1990;4:1275–1277.
- [22] Lifson AR, Hessel NA, Rutherford GW. Progression and clinical outcome of infection due to human immunodeficiency virus. *Clin Infect Dis* 1992;14:966–972.
- [23] Staples CT, Rimland D, Dudas D. Hepatitis C in the HIV Atlanta V.A. cohort study (HAVACS): the effects of co-infection on survival. *Clin Infect Dis* 1999;29:150–154.
- [24] Dorruci M, Pezzotti M, Phillips AN, Lepri AC, Rezza G. Co-infection of hepatitis C virus with immunodeficiency virus and progression to AIDS. *J Infect Dis* 1995;172:1503–1508.
- [25] Piroth L, Duong M, Quantin C, Abrahamowicz M, Michardière R, Aho LS, et al. Does hepatitis C virus co-infection accelerate clinical and immunological evolution of HIV-infected patients? *AIDS* 1998;12:381–388.
- [26] Sabin CA, Telfer P, Phillips AN, Bhagani S, Lee CA. The association between hepatitis C virus and immunodeficiency virus disease progression in a cohort of hemophilic men. *J Infect Dis* 1997;175:164–168.
- [27] Garcia-Samaniego J, Soriano V, Castilla J, Bravo R, Moreno A, Carbo J, et al. Influence of hepatitis C virus genotypes and HIV infection on histological severity of chronic hepatitis C. The hepatitis/HIV spanish study group. *Am J Gastroenterol* 1997;92:1130–1134.
- [28] 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 co-infection. *Lancet* 2000;356:1800–1805.
- [29] Cribier B, Rey D, Schmitt C, Lang JM, Kirn A, Stoll-Keller F. High hepatitis viremia and impaired antibody response in patients co-infected with HIV. *AIDS* 1995;9:1131–1136.
- [30] Sherman KE, O'Brien J, Gutierrez AG, Harrison S, Urdea M, Neuwald P, et al. Quantitative evaluation of hepatitis C virus RNA in patients with concurrent human immunodeficiency virus infections. *J Clin Microbiol* 1993;31:2679–2682.
- [31] Thomas DL, Shih JW, Alter HJ, Vlahov D, Cohn S, Hoover DR, et al. Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. *J Infect Dis* 1996;174:690–695.
- [32] Mazza C, Ravaggi A, Puoti M, Albertini A, Cariani E. Increased HCV titer and absence of selection of E2-hypervariable region (HVR1) in HCV/HIV-co-infection. *J Hepatol* 1994;21:S34.
- [33] Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ. Increasing hepatitis C virus RNA in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. *Blood* 1994;84:1020–1023.
- [34] Danta M, Hui C, Slapak G, Dusheiko G, Johnson M, Sanjay B. Acute HCV in a cohort of HIV-positive men-outcomes and responses to pegylated interferon-alpha 2b and ribavirin. *Hepatology* 2004;40:374A.
- [35] Giovanninni M, Tagger A, Ribero ML, Zuccotti G, Pogliani L, Grossi A, et al. Maternal–infant transmission of hepatitis C virus and HIV infections: a possible interaction. *Lancet* 1990;335:1166.
- [36] Eyster ME, Alter HU, Aledort LM, Quan SM, Halzakis A, Goedert JJ. Heterosexual cotransmission of hepatitis C virus and human immunodeficiency virus. *Ann Intern Med* 1991;115:764–768.
- [37] Martin P, Di Bisceglie AM, Kassianides C, Lisker-Melman M, Hoofnagle JH. Rapidly progressive non-A, non-B hepatitis in patients with human immunodeficiency virus infection. *Gastroenterology* 1989;97:1559–1561.
- [38] Eyster ME, Diamondstone LS, Lien JM. Natural history of hepatitis C virus infection in multitransfused effect of co-infection with human immunodeficiency virus. The multicenter hemophilia cohort study. *J Acquir Immune Defic Syndr* 1993;6:602–610.
- [39] Ridzon R, Gallagher K, Ciesielski C, Mast EE, Ginsberg MB, Robertson BJ, et al. Simultaneous transmission of human immunodeficiency virus and hepatitis C virus from a needle-stick injury. *N Engl J Med* 1997;336:919–922.
- [40] Pol S, Lamorthe B, Trinh Thi N, Thiers V, Carnot F, Zylberberg H, et al. Retrospective analysis of the impact of HIV infection and alcohol use on chronic hepatitis C in a large cohort of drug users. *J Hepatol* 1998;28:945–950.
- [41] Soto B, Sanchez-Quijano A, Rodrigo L, Del Olmo JA, Garcia-Bengoechea 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.
- [42] Rockstroh JK, Spengler U, Sudhop U, Ewig S, Thersen A, Hammerstein U, et al. Immunosuppression may lead to progression of hepatitis C virus associated liver disease in hemophiliacs co-infected with HIV. *Am J Gastroenterol* 1996;91:2563–2568.
- [43] Tolan DJ, Davies MH, Millson CE. Fibrosing cholestatic hepatitis after liver transplantation in a patient with hepatitis C and HIV infection. *N Engl J Med* 2001;345:1781.
- [44] Pol S, Fontaine H, Carnot F, Zylberberg H, Berthelot P, Bréchet C, et al. The natural history of parenterally-acquired chronic hepatitis C. *J Hepatol* 1998;29:12–20.
- [45] Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutelier A, et al. Liver fibrosis progression in HIV–HCV co-infected patients. The Multivirc Group. *Hepatology* 1999;30:1054–1058.
- [46] Law WP, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxruntham K, Lange JM, et al. Impact of viral hepatitis co-infection on response to antiretroviral therapy and HIV disease progression in the HIV–NAT cohort. *AIDS* 2004;18:1169–1177.
- [47] Modapour D, Kary P, Rice CM, Blum HE. Continuous human cell lines inducibly expressing the structural and non structural proteins. *Hepatology* 1998;28:192–201.
- [48] Benhamou Y, Katlama C, Lunel F, Coutellier A, Dohin E, Hamm N, et al. The effects of lamivudine on replication of hepatitis B virus in HIV-infected men. *Ann Intern Med* 1996;125:705–712.
- [49] Benhamou Y, Bochet M, Thibault V, Calvez V, Fievet MH, Vig P, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus. *Lancet* 2001;358:718–723.
- [50] Dore GJ, Cooper DA, Pozniak AL, DeJesus E, Zhong L, Miller MD, et al. 903 study team; 907 study team. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naïve and -experienced patients co-infected with HIV-1 and hepatitis B virus. *J Infect Dis* 2004;189:1185–1192.
- [51] Michelet C, Chaplain JM, Petsaris O, Arvieux C, Ruffault A, Lotteau V, et al. Differential effect of ritonavir and indinavir on immune response to hepatitis C virus in HIV-1 infected patients. *AIDS* 1999;13:1995–1996.

- [52] Rutchmann OT, Negro F, Hirschel B, Hadengue A, Anwar D, Perrin LH. Impact of treatment with human immunodeficiency virus protease inhibitors on hepatitis C viremia in patients co-infected with HIV. *J Infect Dis* 1998;177:783–785.
- [53] Zylberberg H, Chaix ML, Rabian C, Rouzioux C, Brechot C, Viard JP, et al. Anti-HIV tritherapy does not modify HCV replication in co-infected subjects. *Clin Infect Dis* 1998;26:1104–1106.
- [54] Toyoda H, Fukuda Y, Koyama Y, Takamatsu J, Saito H, Hayakawa T. Effect of immunosuppression on composition of quasi-species population of hepatitis C virus in patients with chronic hepatitis C co-infected with human immunodeficiency virus. *J Hepatol* 1997;26:975–982.
- [55] Vento S, Cainelli F, Mirandola F, Cosco L, Di Perri G, Solbiati M, et al. Fulminant hepatitis on withdrawal of chemotherapy in carriers of hepatitis C virus. *Lancet* 1996;347:92–93.
- [56] Gerber MA. Pathobiologic effects of hepatitis C. *J Hepatol* 1995;22:83–86.
- [57] Nelson DR, Marousis CG, Davis GL, Rice CM, Wong J, Houghton M, et al. The role of hepatitis C virus-specific cytotoxic T lymphocytes in chronic hepatitis C. *J Immunol* 1997;158:1473–1481.
- [58] Zylberberg H, Pialoux G, Carnot F, Landau A, Bréchet C, Pol S. Rapidly evolving hepatitis C virus-associated cirrhosis in HIV co-infected patient in relation to antiretroviral tritherapy. *Clin Infect Dis* 1998;27:1255–1258.
- [59] Vento S, Garofano T, Renzini C, Casali F, Ferraro T, Concia E. Enhancement of hepatitis C virus replication and liver damage in HIV-co-infected patients on antiretroviral combination therapy. *AIDS* 1998;12:116–117.
- [60] Carr A, Cooper D. Restoration of immunity to chronic hepatitis B infection in HIV-infected patient on protease inhibitor. *Lancet* 1997;340:995–996.
- [61] John M, Flexman J, French MAH. Hepatitis C virus associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? *AIDS* 1998;12:2289–2293.
- [62] Spengler U, Lichterfeld M, Rockstroh JK. Antiretroviral drug toxicity—a challenge for the hepatologist? *J Hepatol* 2002;36:283–294.
- [63] Zimmerman HJ. Hepatotoxicity. The adverse effects of drugs and other chemicals on the liver. New York: Appleton–Century–Crofts; 1978.
- [64] Danan G. Consensus meetings on causality assessment of drug induced liver injury. *J Hepatol* 1988;7:132–136.
- [65] Aithal GP, Rawlins MD, Day CP. Clinical diagnostic scale: a useful tool in the evaluation of suspected hepatotoxic adverse drug reactions. *J Hepatol* 2000;33:949–952.
- [66] Martinez E, Blanco JL, Arnaiz JA, Perez-Cuevas JB, Mocroft A, Cruceta A, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001;15:1261–1268.
- [67] Lai KK, Gang DL, Zawacki JK, Cooley TP. Fulminant hepatic failure associated with 2',3'-dideoxyinosine (ddI). *Ann Intern Med* 1991;115:283–284.
- [68] Chariot P, Drogou I, de Lacroix-Szmania I, Eliezer-Vanerot MC, Chazaud B, Lombes A, et al. Zidovudine-induced mitochondrial disorder with massive liver steatosis, myopathy, lactic acidosis and mitochondrial DNA depletion. *J Hepatol* 1999;30:156–160.
- [69] Brai N, Leaf HL, Wiczorek RL, Margolis DM. Severe hepatitis in three AIDS patients treated by indinavir. *Lancet* 1997;349:924–925.
- [70] Servoss JC, Sherman KE, Robbins G, Liou S-H, Reisler R, Polsky B, et al. Hepatotoxicity in the US Adult AIDS Clinical Trial Group. *Gastroenterology* 2001;120:A54.
- [71] Saves M, Vandentorren S, Daucourt V, Marimoutou M, Dupon M, Couzigou P, et al. Severe hepatic cytolysis in patients treated by highly active antiretroviral therapy (HAART) with protease inhibitor or with two nucleoside reverse transcriptase inhibitors (NRTIs). *AIDS* 1999;13:145–151.
- [72] Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *J Am Med Assoc* 2000;283:74–80.
- [73] Anonymous. Serious adverse events attributed to nevirapine regimens for post-exposure prophylaxis after HIV exposures-worldwide, 1997–2000. *Morb Mort Wkly Rep*; 2001;49:1153–6.
- [74] Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002;35:182–189.
- [75] Arribas JR, Ibanez C, Ruiz-Antoran B, Pena JM, Esteban-Calvo C, Frias J, et al. Acute hepatitis in HIV-infected patients during ritonavir treatment. *AIDS* 1998;12:1722–1724.
- [76] Lapoile E, Vona G, Canioni D, Carnot F, Chaix M-L, Lagneau J-L, et al. Factors participating in severe HCV-related liver disease in HIV/HCV co-infection. *J Hepatol* 2002;1:609A.
- [77] Romero-Gomez M, Grande L, Nogales MC, Fernandez M, Chavez M, Castro M. Intrahepatic hepatitis C virus replication is increased in patients with regular alcohol consumption. *Dig Liver Dis* 2001;33:698–702.
- [78] Pessione F, Degos F, Marcellin P, Duchatelle V, Njapoum C, Martinot-Peignoux M, et al. Effect of alcohol consumption on serum hepatitis C virus RNA and histological lesions in chronic hepatitis C. *Hepatology* 1998;27:1717–1722.
- [79] Nalpas B, Martin S, Fontaine H, Fabbro-Peray P, Brechot C, Pol S. Impact on medical recommendations on alcohol consumption in HCV positive patients. *J Hepatol* 2001;35:312–313.
- [80] Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998;28:805–809.
- [81] Pol S, Artru P, Thépot V, Berthelot P, Nalpas B. Improvement of the CD4 cell count after alcohol withdrawal in HIV-positive alcoholic patients. *AIDS* 1996;10:1293–1294.
- [82] Prescott LF. Paracetamol, alcohol and the liver. *Br J Clin Pharmacol* 2000;49:291–301.
- [83] Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. *Hepatology* 1995;22:767–773.
- [84] Mallat A, Dhumeaux D. Cocaine and the liver. *J Hepatol* 1991;12:275–278.
- [85] Zhu BL, Oritani S, Shimotouge K, Ishida K, Quan L, Fujita MQ, et al. Methamphetamine-related fatalities in forensic autopsy during 5 years in the southern half of Osaka city and surrounding areas. *H Forensic Sci Int* 2000;113:443–447.
- [86] Reid AE. Nonalcoholic steatohepatitis. *Gastroenterology* 2001;121:710–723.
- [87] Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000;14:25–32.
- [88] Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. *Nat Med* 1995;1:417–422.
- [89] Cote HC, Brumme ZL, Craib KJ, Alexander CS, Wynhoven B, Ting L, et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. *N Engl J Med* 2002;346:811–820.
- [90] Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001;33:1358–1364.

- [91] Serfaty L, Andreani T, Giral P, Carbonel N, Chazouilleres O, Poupon R. Hepatitis C virus induced hypobetalipoproteinemia: a possible mechanism for steatosis in chronic hepatitis C. *J Hepatol* 2001;34:428–434.
- [92] Fultz SL, Justice AC, Chang C. Impact of hepatitis C, HIV, or both on survival in veterans in care before and after the introduction of HAART (abstract 828). In: Program and abstracts of the 10th conference on retroviruses and opportunistic infections, 10–14 February, Boston, MA; 2003.
- [93] Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. *J Am Med Assoc* 2002; 288:199–206.
- [94] Lewden C, Salmon D, Morlat P, Bevilacqua S, Jougla E, Bonnet F, et al. Causes of death among human immunodeficiency virus (HIV)-infected in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. *Int J Epidemiol* 2004;34:121–130.
- [95] Rosenthal E, Pialoux G, Bernard N, Karmochkine M, Rey D, Pradier C, et al. Liver-related mortality in human immunodeficiency virus-infected patients in France (GERMIVIC COHORT STUDY, 1995–2003). *Hepatology* 2004;40:572A.
- [96] Salmon-Ceron D, Lewden C, Morlat P, Bevilacqua S, Jougla E, Bonnet F, et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. *J Hepatol* 2005;42:799–805.
- [97] Camino X, Iribarren JA, Arrizabalga J, Rodriguez F, Von Wichmann AM. Causes of mortality among patients infected with the human immunodeficiency virus in the era of highly active antiretroviral therapy. *Enferm Infecc Microbiol Clin* 2001;19:85–86.
- [98] Puoti M, Spinetti A, Ghezzi A, Donato F, Zaltron S, Putzolu V, et al. Mortality for liver disease in patients with HIV infection: a cohort study. *J Acquir Immune Defic Syndr* 2000;24:211–217.
- [99] Martin-Carbonero L, Soriano V, Valencia ME, Lopez M, Gonzalez-Lahoz J. Impact of chronic viral hepatitis on hospital admission and mortality in HIV-infected patients. *AIDS Res Hum Retroviruses* 2001;17:1467–1471.
- [100] Anderson KB, Guest JL, Rimland D. Hepatitis C virus co-infection increases mortality in HIV-infected patients in the highly active antiretroviral therapy era: data from the HIV Atlanta VA cohort study. *Clin Infect Dis* 2004;39:1507–1513.
- [101] Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-co-infected persons. *N Engl J Med* 2004;351:451–459.
- [102] Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004;351:438–450.
- [103] Laguno M, Murillas J, Blanco JL, Martinez E, Miquel R, Sanchez-Tapias JM, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS* 2004;18:27–36.
- [104] Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *J Am Med Assoc* 2004;292: 2839–2848.
- [105] Tedaldi EM, Baker RK, Moorman AC, Alzola CF, Furhrer J, McCabe RE, et al. Influence of co-infection with hepatitis C virus on morbidity and mortality due to human immunodeficiency virus infection in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2003;36:363–367.