

Management of HCV-Related End-Stage Liver Disease in HIV-Coinfected Patients

Nicolás Merchante¹, Manuel Jiménez-Saenz² and Juan A. Pineda¹

¹Unit of Infectious Diseases, Hospital Universitario de Valme, Seville, Spain; ²Departament of Gastroenterology, Hospital Universitario Virgen Macarena, Seville, Spain

Abstract

End-stage liver disease due to hepatitis C virus has become a major challenge in the management of HIV/HCV-coinfected patients. The diagnosis and management of cirrhosis and its complications in the scenario of HIV/HCV-coinfection are reviewed. Noninvasive approaches to the diagnosis of cirrhosis, such as biomarkers or transient hepatic elastography, may be considered. The clinical profile of cirrhosis decompensation in the coinfecting population is different from that found in HCV-monoinfected individuals. Ascites and hepatic encephalopathy are much more frequent, whereas hepatocellular carcinoma is still uncommon, when simultaneous hepatitis B virus infection is absent. The newest and more conflicting topics on the management of these complications are also discussed. Liver transplantation seems to be a proper option of treatment in HIV/HCV-coinfected patients and should be considered early in their management, since mortality after the first hepatic decompensation is high. (AIDS Rev. 2007;9:131-9)

Corresponding author: Juan A. Pineda, japineda@telefonica.net

Key words

HIV. Hepatitis C virus. End-stage liver disease. Cirrhosis. Liver transplantation.

Introduction

Since the introduction of HAART, liver-related mortality has progressively increased in HIV-infected patients^{1,2}. In fact, liver disease has become the leading cause of death in hepatitis C virus (HCV)/HIV-coinfected patients^{3,4}. Hepatitis C virus-related end-stage liver disease (ESLD) shows an accelerated course in the setting of HIV-coinfection⁵ and the prognosis of decompensated cirrhosis is very poor. Thus, the median survival once decompensation of cirrhosis occurs has been reported to be only 13 months⁶. For these reasons, the management of decompensated cirrhosis and its complications is a challenge for clinicians caring for HIV/HCV-coinfected patients. This is-

sue involves specialists in infectious diseases, hepatologists, internists, surgeons and endoscopists, who should work in coordinated teams. However, the main person responsible for the care for these patients is usually the specialist in infectious diseases. As a consequence of this, the need arises for these specialists to become more familiar with the management of HIV/HCV-coinfected patients with cirrhosis.

This review focuses on the diagnosis and management of cirrhosis and its complications in the scenario of HIV/HCV-coinfection. The use of HAART in this setting is not addressed herein, although it has been reported to improve the survival in these patients⁶. However, the effect of HAART on the progression of liver disease is still a controversial issue. In addition, it has such a number of specific details in these patients that it would deserve a further article. Antiviral therapy of hepatitis C is probably the most effective tool to prevent ESLD in HCV-infected patients^{4,7}. However, its role in infected patients with ESLD, particularly in candidates for transplantation, is still poorly defined. Because of this, it has not been included in this review.

Unfortunately, there is still little knowledge on a number of issues concerning some complications of cir-

Correspondence to:

Juan A. Pineda
Unidad Clínica de Enfermedades Infecciosas
Hospital Universitario Nuestra Sra. de Valme
Ctra. de Cádiz s/n,
Seville 41014, Spain
E-mail: japineda@telefonica.net

rhosis in the specific setting of HIV/HCV-coinfected patients. Until more data are available, it is reasonable to manage these topics as in HCV-monoinfected subjects; even so, the effectiveness of particular measures could be different in the coinfecting population.

Diagnosis of liver cirrhosis

Liver biopsy is still the gold-standard for the diagnosis of liver cirrhosis. Nevertheless, cirrhosis could be diagnosed on the basis of clinical, biochemical and imaging data agreeing with such a diagnosis. Recently, the diagnostic value of four noninvasive predictive models of liver fibrosis based on routine laboratory tests has been evaluated in HIV/HCV-coinfected patients⁸. Among these models, the aspartate aminotransferase (AST) to platelet ratio index (APRI) yielded the best results to rule out cirrhosis, although its positive predictive value was low. An APRI index < 1 has a negative predictive value for cirrhosis of 93%⁸. Due to this, an APRI index > 1 makes a non-histologic diagnosis of cirrhosis unlikely. Another biochemical model proposed for a noninvasive diagnosis of fibrosis in coinfecting patients is the FIB-4 index⁹. The FIB-4 index is calculated according to the following equation: age (years) × AST (U/l) × platelet count (10⁹/l) × alanine aminotransferase (ALT) (U/l)⁹. A FIB-4 value < 1.45 had a negative predictive value of 90% to exclude advanced fibrosis, whereas a value > 3.25 had a positive predictive value of 65% for advanced fibrosis⁹. However, the FIB-4 index, as well other biological models¹⁰, has not been validated to predict cirrhosis.

Transient elastography may have a major role in the diagnosis of cirrhosis in coinfecting patients. In this sense, a liver stiffness value ≤ 14.5 kilopascals (kPa) has negative and a positive predictive value of 94-96% and 83-88%, respectively, for the diagnosis of cirrhosis^{11,12}. In institutions where this technique is available, it can be considered as a noninvasive choice for the diagnosis of cirrhosis. Additionally, liver stiffness measure by transient elastography highly correlates with the presence of severe portal hypertension, assessed by hepatic venous pressure gradient measurement, and with the presence of esophageal varices in HCV-monoinfected individuals^{13,14}. Thus, varices requiring prophylaxis of bleeding are extremely uncommon in patients with stiffness values ≤ 20 kPa¹⁴.

Management of the complications of liver cirrhosis

Ascites

Ascites has been uniformly the most frequent first decompensation of cirrhosis in all surveys conducted

in HIV/HCV-coinfected patients^{4-6,15,16}, being responsible for around 60% of initial hepatic decompensation. This frequency is rather higher than the 23-38% reported in the HCV-monoinfected population^{5,17-19}. The reasons for this remain unclear.

The presence of ascites can be demonstrated with an abdominal paracentesis or an ultrasound examination. An abdominal paracentesis to rule out spontaneous bacterial peritonitis (SBP) should be performed in patients with new-onset or relapsing ascites, in those with signs of infection such as fever, abdominal pain or leukocytosis, and in patients with simultaneous hepatic encephalopathy (HE), gastrointestinal bleeding or renal failure²⁰⁻²².

Low-sodium diet leads to ascites control in some patients and improves the results of other therapies²². Hence, it is considered the first step in the treatment of ascites. In patients with dilutional hyponatremia, consisting in a serum sodium concentration < 130 mEq/l in the presence of ascites, edema or both, daily fluid intake restriction may be necessary²³.

Patients with non-tense ascites may be managed in an outpatient setting with low doses of spironolactone (50 to 200 mg/day)^{20,21}. Concomitant furosemide (20 to 40 mg/day) leads to a higher negative sodium balance, especially if peripheral edema is present^{20,21}. Weight loss of 300 to 500 mg/day in patients without edema and 800 to 1000 mg/day in those with edema can be considered adequate. More intense weight losses may precipitate acute renal failure²¹.

Patients with tense ascites require large-volume paracentesis or high doses of diuretics (maximal daily doses of 400 mg for spironolactone and 160 mg for furosemide), until removal of ascitic fluid. Although there is no difference between both strategies in terms of long-term mortality, large volume paracentesis is usually preferred as it is faster and safer than diuretics^{21,22,24,25}. Irrespective of the initial option chosen, a maintenance regimen of diuretics diminishes the probability of recurrence of ascites²⁶. When large-volume paracentesis with removal of more than five liters of ascitic fluid are used, concomitant administration of intravenous albumin reduces the risk of refractory ascites, hepatorenal syndrome (HRS), dilutional hyponatremia, and death²⁷⁻³³.

Refractory ascites is defined as not responding to high doses of diuretics treatment (400 mg/day of spironolactone and 160 mg/day of furosemide) or that recurs rapidly after paracentesis³⁴. Patients that develop recurrent side effects with low doses of diuretics, such as HE, hyponatremia, hyperkalemia, or renal failure, are also considered to be refractory³⁴. Repeated large-volume paracentesis with albumin infusion is the most widely used option²¹. A meta-analysis³⁵ of five randomized controlled trials compared the use of transjugular intrahepatic portosystemic shunt (TIPS) with repeated large-volume paracentesis in the manage-

ment of refractory ascites. The TIPS were more effective for the control of ascites and were associated with a non-significant trend to improve survival, but they increased the risk of HE. Another more recent meta-analysis³⁶ confirmed these results and showed a significant improvement in transplant-free survival and a reduction in the prevalence of portal hypertension-related complications treated with TIPS. However, two main drawbacks should be kept in mind when considering this therapeutic option: the high rate of obstruction of TIPS, which probably will be minimized with the generalized use of covered stents, and the irreversible deterioration of liver function that may be triggered. An adequate selection of patients (younger than 60 years, bilirubin < 3 mg/dl, serum sodium > 130 mEq/l and absence of cardiac dysfunction) is critical as it probably may optimize the results, although it also reduces its applicability to a limited subset of cirrhotic patients with refractory ascites.

Hepatorenal syndrome

Hepatorenal syndrome is a complication of ESLD, occurring mainly in patients with advanced cirrhosis and ascites with marked systemic circulatory dysfunction. Renal failure in HRS is functional and caused by intense vasoconstriction of the renal circulation, which leads to a pronounced reduction in glomerular filtration rate, in the setting of extrarenal arterial vasodilatation. Bacterial infections, primarily SBP, are the most common trigger for the development of HRS. The prognosis of HRS is very poor. It was the second cause of death due to liver disease in a recent survey conducted in HIV/HCV-coinfecting patients undergoing HAART⁴. Once HRS is suspected, it is important to rule out volume depletion with a trial of plasma volume expansion with albumin during at least two days. Diagnostic criteria of HRS have been recently revised by the International Ascites Club and these are depicted in table 1³⁷.

The only effective therapeutic option is liver transplantation. In the meantime, albumin infusion plus administration of vasoactive drugs, such as octreotide plus midodrine or terlipressin, may achieve a complete reversal of renal failure by expansion of the central blood volume³⁷. Namely, terlipressin may lead to a complete response in 60% of patients and to improve the short-term survival³⁷. However, recurrence after treatment discontinuation is very frequent and up to 5-10% may develop severe side effects³⁷. The experience with TIPS in this setting is much more limited.

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is the infection of ascitic fluid in the absence of an evident intraabdomi-

Table 1. Diagnostic criteria of hepatorenal syndrome in cirrhosis of the International Ascites Club

Cirrhosis with ascites.
Serum creatinine > 1.5 mg/dl.
No improvement of serum creatinine (decrease to a level of 1.5 mg/dl or less) after at least two days with diuretic withdrawal and volume expansion with albumin.
Absence of shock.
No current or recent treatment with nephrotoxic drugs.
Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria (> 50 red blood cells per high power field) and/or abnormal renal ultrasonography.

nal source of infection. An absolute polymorphonuclear leukocyte count ≥ 250 cells/ml in the ascitic fluid or a positive culture are diagnostic of SBP³⁸. The clinical and microbiological characteristics of SBP in HIV/HCV-coinfecting patients seem to be quite similar to those observed in non HIV-infected cirrhotic subjects, except for more frequent isolation of the causative agent and a higher incidence of pneumococcal infection³⁹. Short-term survival after an episode of SBP in HIV-infected patients is very poor³⁹. Impaired renal function at diagnosis of SBP is associated with a poorer prognosis³⁹.

Patients with SBP should receive empiric antibiotic therapy whereas antibiogram is available^{20-22,38}. Intravenous cefotaxime (2 g every eight hours during five days) is usually the preferred regimen^{20-22,38}. However, no study published so far has specifically evaluated what is the best empiric antibiotic regimen for HIV/HCV-coinfecting patients with SBP. As *Escherichia Coli* and *Streptococcus pneumoniae* seem to be responsible for most of the cases of SBP in HIV-infected patients³⁹, third-generation cephalosporins are a proper option in HIV/HCV-coinfecting patients, although pneumococcal resistance is a serious concern. Concomitant intravenous albumin infusion (1.5 g/kg body weight on day 1 and 1 g/kg on day 3) reduced mortality from 29 to 10% in a controlled randomized trial⁴⁰. Because HRS almost exclusively occurs in patients with serum bilirubin > 4 mg/dl and serum creatinine > 1 mg/dl, some experts suggest that the prophylactic use of albumin could be restricted to these patients³⁷.

In a meta-analysis of eight randomized trials, antibiotic prophylaxis in cirrhotic patients with upper gastrointestinal bleeding was associated with a reduction in mortality and incidence of bacterial infections without significant adverse events⁴¹. Based on these data, primary prophylaxis of SBP is recommended in those patients with liver cirrhosis suffering from upper gas-

gastrointestinal bleeding²¹. Norfloxacin 400 mg twice daily for seven days has been the preferred regimen. However, in a recent randomized controlled trial⁴² that compared oral norfloxacin versus intravenous ceftriaxone in the prophylaxis of bacterial infections in patients with gastrointestinal hemorrhage and severe liver failure, 33% of patients on norfloxacin developed bacterial infections versus 11% in the ceftriaxone arm. These results need to be confirmed by further studies, as does its correlation in HIV/HCV-coinfected patients, since HIV infection was an exclusion criteria in this trial. In patients who survive an episode of SBP long-term secondary prophylaxis with norfloxacin 400 mg/day prevents relapses⁴³. In cirrhotic patients with low protein ascites (< 1.5 g/l) and advanced liver failure or impaired renal function, prophylaxis with norfloxacin has been reported very recently to be associated with a reduction in the probability of developing HRS or SBP and an increase in the survival at one year⁴⁴.

Portal hypertensive gastrointestinal bleeding

Portal hypertensive gastrointestinal bleeding has been a relatively uncommon type of decompensation of cirrhosis in most of the surveys conducted in HIV/HCV-coinfected patients, both as the first event and as the cause of death^{4-6,15,16}. The reasons for this lower frequency in this population remain to be clarified. Due to this, it should not be assumed that screening of esophageal varices in these patients is cost-effective, as in HCV-monoinfected individuals^{45,46}. However, until more evidence becomes available, it is reasonable to screen HIV/HCV-coinfected patients with cirrhosis for the presence of esophageal varices in a similar way to HCV-monoinfected patients. Thus, gastroesophageal endoscopy is to be performed at diagnosis of cirrhosis. If no varices are found, it will be repeated after 2-3 years if a clinical decompensation occurs, or if signs of portal hypertension such as thrombocytopenia, spleen enlargement, or ultrasound findings appear⁴⁶. In patients with small varices, endoscopy may be repeated every 1-2 years as the risk of bleeding is very low⁴⁶.

Primary prophylaxis of variceal bleeding is indicated in those subjects with large varices (F2 and F3), and in those with small varices (F1) but with red wale signs or being at Child-Turcotte-Pugh (CTP) class C^{45,46}. Non-selective beta-blockers are the preferred therapeutic option as they reduce the risk of bleeding⁴⁷⁻⁵³. However, their effect on mortality is uncertain. Endoscopic band ligation (EBL) is a choice in patients with large varices and contraindications or intolerance to beta-blockers as they have demonstrated comparable effectiveness in clinical trials⁵⁴⁻⁵⁷. Moreover, EBL seems to be more cost-effective than beta-blockers,

provided that cost per quality-adjusted life year is considered⁵⁸.

In patients surviving a first bleeding episode, secondary prophylaxis should be considered shortly thereafter⁴⁵. The rate of rebleeding with the combination of beta-blockers plus EBL was lower than with EBL alone in two randomized trials^{59,60}. Thus, beta-blockers plus EBL is the most adequate option in this setting^{45,46}. Recently, the efficacy of the combination of beta-blockers and an aggressive protocol of EBL of varices, which consists in EBL after the initial bleeding of any visible varix during the follow-up, irrespective of its size, has been reported. There were no cases of rebleeding among 118 patients treated with this strategy after a median follow-up of 16 months⁶¹. If endoscopic and pharmacologic treatments fail, TIPS may be used^{45,46}. In a recent meta-analysis⁶², the rate of rebleeding was lower with the use of TIPS when compared with endoscopic therapy, while there were no differences in terms of mortality. However, the median (range) rate of dysfunction or occlusion of the shunt was 59% (18-72%) and the risk of HE was also higher. For these reasons, TIPS is currently considered as an alternative therapy to beta-blockers and EBL. Distal splenorenal shunt was as effective as TIPS in patients with CTP class A or B and refractory bleeding in a recent randomized trial⁶³.

Hepatic encephalopathy

The incidence of HE is high in HIV/HCV-coinfected patients, accounting for 27-28% of the first complications of cirrhosis^{4-6,15,16}. This figure is far from the 1-8% reported in monoinfected subjects^{5,17-19}. Furthermore, HE is the leading cause of liver-related mortality in the HIV/HCV-coinfected population under HAART, causing half of the liver-related deaths⁴. Finally, HE is a strong predictor of poor prognosis, as the median survival after an episode of HE is only three months in HIV/HCV-coinfected patients with ESLD⁶. The reasons for this increased incidence of HE in the HIV/HCV-coinfected population are unclear. Consumption of depressors of central nervous system, which is frequent among HIV-infected individuals, or a higher frequency of bacterial infections could partly explain these differences.

Hepatic encephalopathy more commonly presents as an acute episode, usually triggered by one or more precipitant factors such as portal hypertensive gastrointestinal bleeding, acute renal failure, electrolyte disturbances, diuretics, depressors of central nervous system, constipation, SBP and other infections⁶⁴. For this reason, management of HE should be focused on investigating and treating the triggering factors. Specifically, in patients receiving diuretics these should be

temporarily discontinued if renal failure or electrolyte abnormalities occur⁶⁴. If benzodiazepine or opioid substances consumption is suspected, flumazenil or naloxone, respectively, may be used. Spontaneous bacterial peritonitis should be ruled out in those subjects with HE and ascites⁶⁴. Ammonia is believed to be the key factor in the pathogenesis of overt HE in patients with cirrhosis. Due to their presumed ability to reduce blood ammonia levels, nonabsorbable disaccharides (lactulose and lactitol) have been considered the standard treatment for HE⁶⁵. However, a systematic review of 22 randomized trials that compared lactulose or lactitol versus placebo, no treatment or antibiotics was not able to demonstrate a beneficial effect of them on HE⁶⁶. These results have led to some skepticism about the real efficacy of this intervention⁶⁷. However, the inconclusive results of the trials should be interpreted with caution, as some confounding variables such as the degree of liver failure, the nature of the precipitating event, or the extent of portal-systemic shunting have not been well controlled in many surveys⁶⁸. In addition, lactulose may improve cognitive functions in patients with minimal HE⁶⁹. This controversy reflects that lactulose probably still has a role in the treatment of HE, although well-designed clinical trials are awaited. In the same manner, the efficacy of other measures in HE such as protein restriction⁷⁰, neomycin^{71,72} or rifaximin⁷³ remains controversial. Benzodiazepine receptor antagonists do not provide any benefit in the management of HE, out of the acute benzodiazepine intoxication⁷⁴.

Hepatocellular carcinoma

The available data regarding the current incidence of hepatocellular carcinoma (HCC) in HIV/HCV-coinfected patients are scarce and conflicting. Some investigations have suggested that HIV shortens the time from HCV infection to the development of HCC⁷⁵⁻⁷⁷. According to this, the risk of developing HCC should be increased in HIV/HCV-coinfected patients. However, the incidence of HCC in coinfecting patients seems to be currently lower than in HCV-monoinfected patients. In one retrospective cohort study conducted in HCV-infected patients with and without advanced liver disease in the HAART and pre-HAART era, HIV did not increase the risk of developing HCC, irrespective of the period of time considered⁷⁸. In another survey, among 1217 patients with HCV-related ESLD, 180 of them being HIV-coinfected, the incidence of HCC was significantly lower in the coinfecting group⁷⁹. Other cohort studies have shown similar results^{15,16}. By contrast, one case-control study suggested that HCC is diagnosed at a younger age and shows a more advanced stage at diagnosis in HIV/HCV-coinfected

individuals than in HCV-monoinfected ones⁸⁰. However, this apparent contradiction may be due to the higher prevalence of concomitant HBV coinfection in the latter study. The reasons for the current lower incidence of HCC among coinfecting patients are unclear. It is likely that HIV shortens the survival of patients with HCV-related ESLD to such an extent that HCC, a late complication of liver cirrhosis⁸¹, has not had a chance to emerge. Due to this, some experts have suggested that the incidence of HCC could increase in the next years as a consequence of the effect of HAART on survival⁸². Accordingly, a fivefold increase of deaths due to HCC among HIV individuals was reported in France during the period 1995-2001⁸³. For these reasons, HCC will likely be a more relevant problem in the near future.

The benefit yielded by HCC surveillance programs in HIV-infected patients with cirrhosis due to HCV has not been assessed. The assumption that they are cost-effective, based on data coming from HCV-monoinfected patients, might not be proper if we consider that the current incidence of HCC in these individuals is lower. While further data on this topic is to come, in our opinion HIV/HCV-coinfecting patients with cirrhosis may be routinely screened for the presence of HCC with an alpha-fetoprotein (AFP) determination and an ultrasound examination every six months, as is recommended in HCV-monoinfected individuals⁸⁴. If lesions < 10 mm are identified, the surveillance interval should be shortened to three months.

Diagnosis of HCC is based on radiology, biopsy and AFP determination. The diagnostic approach varies depending on the size of the lesion. The algorithm proposed by Bruix and Sherman for the evaluation of a nodule found on ultrasound during screening can be useful for this purpose (Fig. 1)⁸⁴.

Surgical therapy of HCC includes liver resection and transplantation. Hepatic resection is indicated in solitary tumors < 5 cm in diameter without vascular invasion or extrahepatic spread, with preserved liver function (CTP class A or B) and without portal hypertension⁸⁴, but extensive experience with surgical resection is lacking in HIV/HCV-coinfecting patients. Liver transplantation is the choice for single tumors < 5 cm that are not candidates to resection and when there are up to three nodules < 3 cm, without vascular invasion or metastasis⁸⁴. Promising results with liver transplantation in a small cohort of coinfecting patients have been recently reported⁸⁵. In patients with solitary tumors < 3 cm who are not candidates for resection or transplantation, radiofrequency or alcohol percutaneous ablation is the preferred option⁸⁴. Non-curative therapies include transarterial embolization and chemoembolization and are recommended for single nodules > 3 cm or multifocal HCC without vascular invasion or extrahepatic spread⁸⁴.

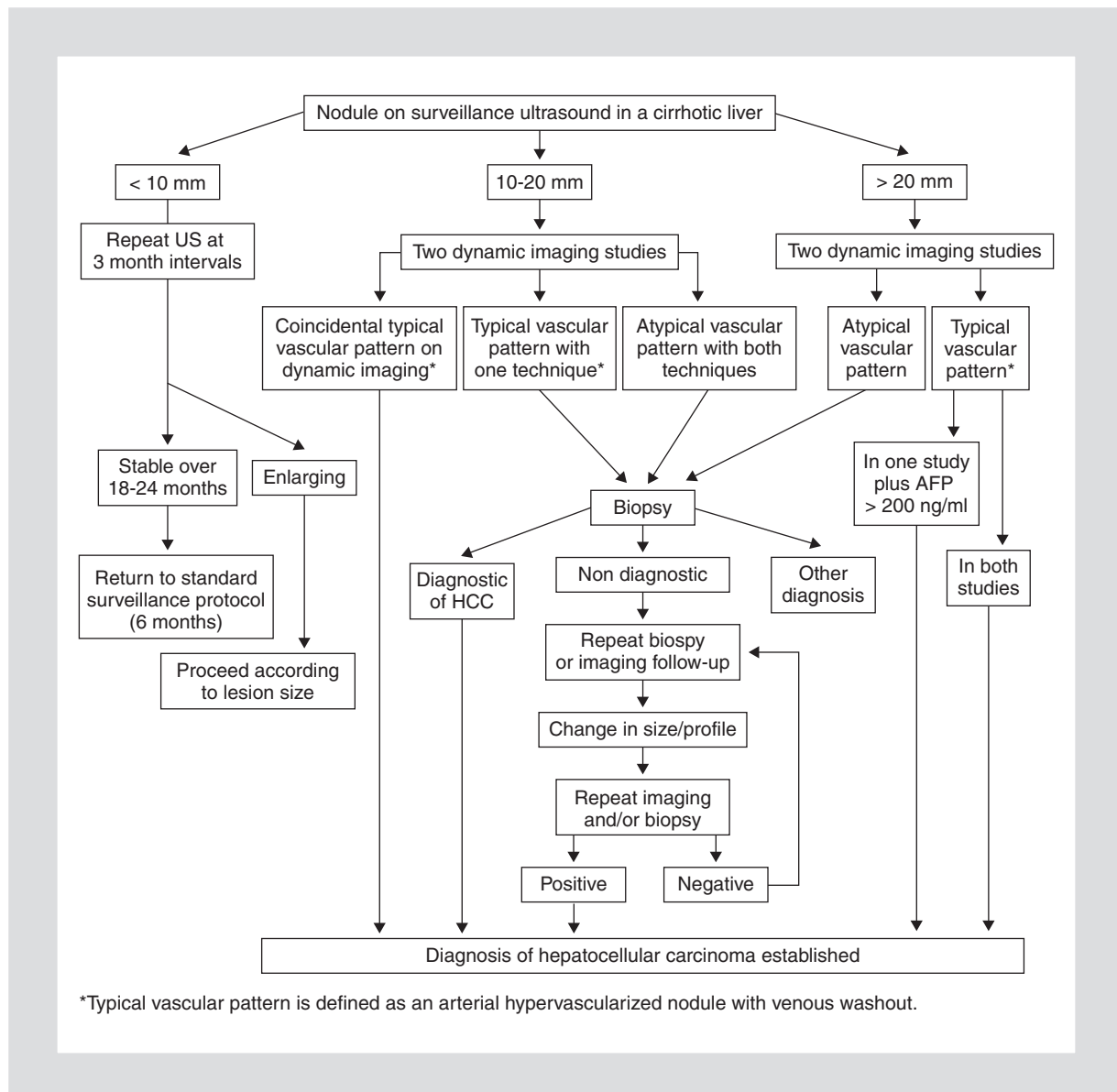


Figure 1. Algorithm for investigation of a nodule found on ultrasound during screening. AFP: alpha-fetoprotein; HCC: hepatocellular carcinoma (adapted from Bruix and Sherman⁸⁴).

Liver transplantation

Since the widespread use of HAART, the short- and medium-term survival of HIV-infected patients receiving liver transplantation has markedly improved⁸⁶. As a consequence of this, liver transplantation has become an option of treatment in HIV/HCV-coinfected patients with ESLD^{87,88}. The first prospective study of liver transplantation in the HAART era was undertaken in San Francisco (USA) with promising survival rates, as nine of 10 patients survived after a median follow-up of 480 days⁸⁹. However, only four (40%) of the liver recipients were coinfecting with HCV in that cohort. In Spain, 65 liver transplantations have been performed

from 2002 to 2006⁹⁰. Twelve (18%) deaths occurred after a median follow-up of 12 months. The survival rates (95% CI) at one, two, and three years were 88% (74-94%), 77% (59-88%) and 66% (43-81%), respectively. Similar results have been reported in France⁹¹ and from the University of Pittsburgh⁹². However, HCV recurrence is universal and rapid progression of fibrosis may occur in up to 40% patients at five years. The role that therapy with pegylated interferon plus ribavirin may play in controlling recurrent hepatitis C is currently under evaluation^{93,94}.

The protocols currently used to include HIV-infected patients in liver transplantation programs consider the same hepatic criteria as in general population^{87,95}. This

Table 2. Criteria for considering liver transplantation in HIV-infected patients in Spain

Liver-related
Child-Turcotte-Pugh stage B or C.
One of the following clinical decompensation:
– Hepatic encephalopathy.
– Refractory ascites.
– Hepatorenal syndrome.
– Uncontrolled portal gastrointestinal bleeding.
– Spontaneous bacterial peritonitis.
– Early stage hepatocellular carcinoma.
– Severe malnutrition.
HIV-related
Clinical criteria:
– None of AIDS-defining opportunistic infections, except tuberculosis, esophageal candidiasis or <i>P. jiroveci</i> pneumonia.
Immunologic criteria:
– CD4 cell count > 100 cells/ μ l.
– Patients who have suffered from tuberculosis, esophageal candidiasis or <i>P. jiroveci</i> pneumonia must have a CD4 cell count > 200 cells/ μ l.
– Patients who do not fulfill the criteria for starting HAART must have a CD4 cell count > 350 cell/ μ l.
Virologic criteria:
– Undetectable viral load (< 50 copies/ml) at the time of the transplant or have effective and durable therapeutic options for HIV infection during the posttransplant period.
General criteria
Abstinence for drugs (heroin and cocaine) for at least two years.
No consumption of alcohol for at least six months.
Favorable psychiatric evaluation.
Understanding of the technique.
Social stability.
Woman must not be pregnant.

could be a drawback since some relevant factors that strongly influence the hepatic outcome in HIV/HCV-coinfected patients, such as HE or CD4 cell count, are not taken into account. Moreover, the predictive value of

MELD score for survival in the HIV-infected population may be lower than in HIV-uninfected patients^{6,96,97}. In this sense, it has been reported that 25% of HIV-infected patients who are potential candidates for liver transplantation die while in the waiting list or during the evaluation process⁹⁸. Nevertheless, these data probably also reflect that referral to liver transplantation evaluation is still not a common practice among physicians caring for HIV-infected patients. Data on the optimal timing for liver transplantation and specific prognostic scores for HIV-infected patients are needed.

The current criteria for considering liver transplantation in HIV/HCV-coinfected patients in Spain are summarized in table 2^{99,100}. The updated HIV-specific criteria for liver transplant candidates in the USA are published elsewhere⁹². They do not significantly differ from Spanish recommendations, with the exception of the previous opportunistic complications allowed. Namely, the only opportunistic complications excluded in the U.S. criteria are progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis and multidrug-resistant systemic fungal infections, as authors consider that the remaining opportunistic infections can be efficaciously treated and prevented⁹².

Conclusions

End-stage liver disease is a leading cause of morbidity and mortality in HIV/HCV-coinfected patients. The clinical profile of decompensated cirrhosis in the coinfecting population is different from that found in HCV-monoinfected individuals. Ascites and HE are much more frequent, whereas HCC seems to be rare. Liver transplantation should be considered early in the management of these patients, since mortality after the first hepatic decompensation is high.

References

1. Mocroft A, Brettle R, Kirk O, et al. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. *AIDS* 2002;16:1663-71.
2. Macias J, Melguizo I, Fernández-Rivera F, et al. Mortality due to liver failure and impact on survival of hepatitis virus infections in HIV-infected patients on potent antiretroviral therapy. *Eur J Clin Microbiol Infect Dis* 2002;21:775-81.
3. Salmon-Ceron D, Lewden C, Morlat P, et al. Liver disease as major cause of death among HIV-infected patients: role of hepatitis C and B viruses and alcohol. *J Hepatol* 2005;42:799-805.
4. Pineda J, García-García J, Aguilar-Guisado M, et al. Clinical progression of HCV-related chronic liver disease in HIV-infected patients undergoing HAART. *Hepatology* [In press].
5. Pineda J, Romero-Gómez M, Díaz-García F, et al. HIV coinfection shortens the survival of patients with HCV-related decompensated cirrhosis. *Hepatology* 2005;41:779-89.
6. Merchante N, Girón-González J, González-Serrano M, et al. Survival and prognostic factors of HIV-infected patients with HCV-related end-stage liver disease. *AIDS* 2006;20:49-57.
7. Soriano V, Maida I, Núñez M, et al. Long-term follow-up of HIV-coinfected patients with chronic HCV infection treated with interferon-based therapies. *Antivir Ther* 2009;9:987-92.

8. Macías J, Girón-González J, González-Serrano M, et al. Prediction of liver fibrosis in HIV/HCV-coinfected patients by simple noninvasive indexes. *Gut* 2006;55:409-14.
9. Sterling R, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006;43:1317-25.
10. Kelleher T, Mehta S, Bhaskar R, et al. Prediction of hepatic fibrosis in HIV/HCV coinfection patients using serum fibrosis markers: the SHASTA index. *J Hepatol* 2005;43:78-84.
11. de Ledinghen V, Douvin C, Kettaneh A, et al. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/HCV-coinfected patients. *J Acquir Immune Defic Syndr* 2006;41:175-9.
12. Vergara S, Macías J, Rivero A, et al. The utility of transient elastometry in assessing liver fibrosis in patients with HIV/HCV coinfection. *Clin Infect Dis* 2007 [in press].
13. Vizzutti F, Arena U, Romanelli R, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology* 2007;45:1290-7.
14. Kazemi F, Kettaneh A, N'kontchou G, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large esophageal varices. *J Hepatol* 2006;45:230-5.
15. Bruno R, Sacchi P, Patrono S, Maiocchi L, Filice G. Hierarchy of liver related major complications in a cohort of coinfection patients with compensated liver cirrhosis [abstract 873]. In: Program and abstracts of the 13th CROI (Denver, CO). February 2006.
16. Miró J, Murillas J, Laguno M, et al. Natural history and prognosis of end-stage liver disease (ESLD) in Spanish HIV-1 infected patients: A prospective cohort study of 104 patients (1999-2004) [abstract PS7/1]. In: Program and abstracts of the 10th European AIDS Conference (Dublin, Ireland). November 2005.
17. Planas R, Balleste B, Alvarez M, et al. Natural history of decompensated HCV-related cirrhosis. A study of 200 patients. *J Hepatol* 2004;40:823-30.
18. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463-72.
19. Sangiovanni A, Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to HCV: A 17-year cohort study of 214 patients. *Hepatology* 2006;43:1303-10.
20. Ginés P, Cárdenas A, Arroyo V, Rodés J. Management of cirrhosis and ascites. *N Engl J Med* 2004;350:1646-54.
21. Runyon B. Management of adult patients with ascites due to cirrhosis. *Hepatology* 2004;39:841-56.
22. Runyon B. Ascites and spontaneous bacterial peritonitis. In: Sleisenger and Fordtran's *Gastrointestinal and Liver Disease*. 7th ed. Feldman M, Friedman LS, Sleisenger MH (eds). Philadelphia: Saunders; 2002:1517-42.
23. Gines P, Berl T, Bernardi M, et al. Hyponatremia in cirrhosis: from pathogenesis to treatment. *Hepatology* 1998;28:851-64.
24. Ginés P, Arroyo V, Quintero E, et al. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites: results of a randomized study. *Gastroenterology* 1987;93:234-41.
25. Salerno F, Badalamenti S, Incerti P, et al. Repeated paracentesis and IV albumin infusion to treat 'tense' ascites in cirrhotic patients: a safe alternative therapy. *J Hepatol* 1987;5:102-8.
26. Fernández-Esparrach G, Guevara M, Sort P, et al. Diuretic requirements after therapeutic paracentesis in non-azotemic patients with cirrhosis: a randomized double-blind trial of spironolactone versus placebo. *J Hepatol* 1997;26:614-20. [Erratum, *J Hepatol* 1997;26:1430].
27. Tito L, Gines P, Arroyo V, et al. Total paracentesis associated with intravenous albumin management of patients with cirrhosis and ascites. *Gastroenterology* 1990;98:146-51.
28. Ginés P, Tito L, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology* 1988;94:1493-502.
29. Panos M, Moore K, Vlavianos P, et al. Single, total paracentesis for tense ascites: sequential hemodynamic changes and right atrial size. *Hepatology* 1990;11:662-7.
30. Pozzi M, Osculati G, Boari G, et al. Time course of circulatory and humoral effects of rapid total paracentesis in cirrhotic patients with tense, refractory ascites. *Gastroenterology* 1994;106:709-19.
31. Ginés A, Fernández-Esparrach G, Monescillo A, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology* 1996;111:1002-10.
32. Luca A, García-Pagan JC, Bosch J, et al. Beneficial effects of intravenous albumin infusion on the hemodynamic and humoral changes after total paracentesis. *Hepatology* 1995;22:753-8.
33. Ruiz-del-Arbol L, Monescillo A, Jiménez W, García-Plaza A, Arroyo V, Rodes J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterology* 1997;113:579-86.
34. Arroyo V, Gines P, Gerbes A, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* 1996;23:164-76.
35. D'Amico G, Luca A, Morabito A, Miraglia R, D'Amico M. Uncovered transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis. *Gastroenterology* 2005;129:1282-93.
36. Salerno F, Camma C, Enea M, Rössle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: A meta-analysis of individual patient data. *Gastroenterology* [in press].
37. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of the hepatorenal syndrome in cirrhosis. A consensus workshop of the international ascites club. *Gut* [in press].
38. Rimola A, García-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. *J Hepatol* 2000;32:142-53.
39. Shaw E, Castellote J, Santín M, et al. Clinical features and outcome of spontaneous bacterial peritonitis in HIV-infected cirrhotic patients: a case control study. *Eur J Clin Microbiol Infect Dis* 2006; 25:291-8.
40. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341:403-9.
41. Soares-Weiser K, Brezis M, Tur-Kaspa R, Leibovici L. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. *Cochrane Database Syst Rev* 2002;2:CD002907.
42. Fernández J, Ruiz del Arbol L, Gómez C, et al. Norfloxacin vs. ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology* 2006;131:1049-56.
43. Gines P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990;12:716-24.
44. Fernández J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* [in press].
45. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005;43:167-76.
46. Bosch J. Documento de consenso sobre Hipertensión Portal de la Asociación Española para el Estudio del Hígado. Available at: www.aeeh.org.
47. Pascal J, Cales P. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. *N Engl J Med* 1987;317:856-61.
48. Ideo G, Bellati G, Fesce E, Grimoldi D. Nadolol can prevent the first gastrointestinal bleeding in cirrhotics: A prospective, randomized study. *Hepatology* 1988;8:6-9.
49. Lebrech D, Poynard T, Capron J, et al. Nadolol for prophylaxis of gastrointestinal bleeding in patients with cirrhosis. A randomized trial. *J Hepatol* 1988;7:118-25.
50. The Italian Multicenter Project for Propranolol in Prevention of Bleeding. Propranolol prevents first gastrointestinal bleeding in non-ascitic cirrhotic patients. Final report of a multicenter randomized trial. *J Hepatol* 1989;9:75-83.
51. Conn H, Grace N, Bosch J, et al. Propranolol in the prevention of the first hemorrhage from esophagogastric varices: A multicenter, randomized clinical trial. *Hepatology* 1991;13:902-12.
52. Andreani T, Poupon R, Balkau B, et al. Preventive therapy of first gastrointestinal bleeding in patients with cirrhosis: results of a controlled trial comparing propranolol, endoscopic sclerotherapy and placebo. *Hepatology* 1990;12:1413-9.
53. Hayes P, Davis J, Lewis J, Bouchier I. Meta-analysis of the value of propranolol in the prevention of variceal hemorrhage. *Lancet* 1990;336:153-6.
54. Sarin S, Lamba G, Kumar M, Misra A, Murthy N. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 1999;340:988-93.
55. Lui H, Stanley A, Forrest E, et al. Primary prophylaxis of variceal hemorrhage: A randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. *Gastroenterology* 2002;123:735-44.
56. Jutabha R, Jensen D, Martin P, Savides T, Han S-H, Gornbein J. Randomized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high risk esophageal varices. *Gastroenterology* 2005;128:870-81.

57. Schepke M, Kleber G, Nurnberg D, et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2004;40:65-72.
58. Imperiale T, Klein R, Chalasani N. Cost-effectiveness analysis of variceal ligation versus beta-blockers for primary prevention of variceal bleeding. *Hepatology* 2007;45:870-8.
59. Lo G, Lai K, Cheng J, et al. Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal rebleeding: a prospective, randomized trial. *Hepatology* 2000;32:461-5.
60. de la Pena J, Brullet E, Sánchez-Hernandez E, et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. *Hepatology* 2005;41:572-8.
61. Flamm S, Branch-Elliman W, Sled S. Aggressive endoscopic band ligation dramatically reduces rates of recurrent variceal bleeding in patients with portal hypertension: a retrospective cohort study. In: Program and Abstracts of the Digestive Disease Week 2007, 19-24 May, Washington, DC, USA [abstract 173e].
62. Khan S, Tudur Smith C, Williamson P, Sutton R. Portosystemic shunts versus endoscopic therapy for variceal rebleeding in patients with cirrhosis. *Cochrane Database Syst Rev* 2006;4:CD000553.
63. Henderson J, Boyer T, Kutner M, et al. Distal splenorenal shunt versus transjugular intrahepatic portal systematic shunt for variceal bleeding: a randomized trial. *Gastroenterology* 2006;130:1643-51.
64. Weissenburn K. Clinical features of hepatic encephalopathy. In: *Hepatology. A textbook of liver disease*. 4th ed. Zakim & Boyer (eds). Philadelphia: Saunders; 2003:431-44.
65. Blei A, Cordoba J. Hepatic encephalopathy. *Am J Gastroenterol* 2001;96:1968-76.
66. Als-Nielsen B, Gluud L, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomized trials. *BMJ* 2004;328:1046-50.
67. Shawcross D, Jalan R. Dispelling myths in the treatment of hepatic encephalopathy. *Lancet* 2005;365:431-3.
68. Blei A. Treatment of hepatic encephalopathy. *Lancet* 2005;365:1383-4.
69. Prasad S, Dhiman R, Duseja A, Chawla Y, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. *Hepatology* 2007;45:549-59.
70. Córdoba J, Lopez-Hellin J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. *J Hepatol* 2004;41:38-43.
71. Conn H, Leevy C, Vlacevic Z, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. *Gastroenterology* 1977;72:573-83.
72. Atterbury C, Maddrey W, Conn H. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. *Am J Dig Dis* 1978;23:398-406.
73. Mas A, Rodes J, Sunyer L, et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. *J Hepatol* 2003;38:51-8.
74. Als-Nielsen B, Gluud L, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy. *Cochrane Database Systematic Review* 2004;2:CD002798.
75. Garcia-Samaniego J, Rodriguez M, Berenguer J, et al. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am J Gastroenterol* 2001;96:179-83.
76. Davila J, Morgan R, Shaib Y, McGlynn K, El Serag H. Hepatitis C infection and the increased incidence of hepatocellular carcinoma: a population-based study. *Gastroenterology* 2004;127:1372-80.
77. Puoti M, Bruno R, Soriano V, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS* 2004;18:2285-93.
78. Kramer J, Giordano T, Souček J, Richardson P, Hwang L, El Serag H. The effect of HIV coinfection on the risk of cirrhosis and hepatocellular carcinoma in U.S. Veterans with hepatitis C. *Am J Gastroenterol* 2005;100:56-63.
79. García-García J, Romero-Gómez M, Girón-González J, et al. Incidence of and factors associated with hepatocellular carcinoma among HCV and HIV coinfecting patients with decompensated cirrhosis. *AIDS Res Hum Retroviruses* 2006;22:1236-41.
80. Puoti M, Bruno R, Soriano V, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS* 2004;18:2285-93.
81. Castells L, Vargas V, González A, Esteban J, Esteban R, Guardia J. Long interval between HCV infection and development of hepatocellular carcinoma. *Liver* 1995;15:159-63.
82. Bruno R, Puoti M, Sacchi P, Filice C, Carosi G, Filice G. Management of hepatocellular carcinoma in HIV-infected patients. *J Hepatol* 2006;44(Suppl 1):146-50.
83. Rosenthal E, Poiree M, Pradier C, et al. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS* 2003;17:1803-9.
84. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208-36.
85. Di Benedetto F, De Ruvo N, Berretta M, et al. Hepatocellular carcinoma in HIV patients treated by liver transplantation. *Eur J Surg Oncol* [in press].
86. Ragni M, Belle S, Im K, et al. Survival of HIV-infected liver transplant recipients. *J Infect Dis* 2003;188:1412-20.
87. García-Samaniego J, Soriano V, Miró J, et al. Management of chronic viral hepatitis in HIV-infected patients: Spanish consensus conferences. *HIV Clin Trials* 2002;3:99-114.
88. Soriano V, Puoti M, Sulkowski M, et al. Care of patients with hepatitis C and HIV coinfection. *AIDS* 2004;18:1-12.
89. Roland M, Carlson L, Terrault N, et al. Patient and graft outcomes following solid organ transplantation [abstract 826]. In: Program and abstracts of the 11th CROI (San Francisco, CA). February 2004.
90. Miró J. Organ transplantation in HIV-infected patients - management and outcome experiences from Europe and North America [abstract PL6.3]. In: Program and abstracts of the 8th International Congress on Drug Therapy in HIV infection (Glasgow, UK). November 2006.
91. Duclos-Vallee J, Feray C, Sebagh M, et al. Survival and prognostic factors in a large cohort of HIV-HCV coinfecting patients transplanted in a single centre [abstract 772]. In: Program and abstracts of the 57th Annual Meeting of the American Association for the Study of Liver Diseases (Boston, MA). October 2006.
92. Roland M, Stock P. Liver transplantation in HIV-infected recipients. *Semin Liver Dis* 2006;26:273-84.
93. Castells L, Esteban J, Bilbao I, et al. Early antiviral treatment of HCV recurrence after liver transplantation in HIV-infected patients. *Antivir Ther* 2006;11:1061-70.
94. Wojcik K, Vogel M, Voigt E, et al. Antiviral therapy for HCV recurrence after liver transplantation in HIV-infected patients: outcome in the Bonn cohort. *AIDS* 2007;21:1363-5.
95. Soriano V, Miró J, García-Samaniego J, et al. Consensus conference on chronic viral hepatitis and HIV infection: updated Spanish recommendations. *J Viral Hepat* 2004;11:2-17.
96. Terrault N, Carter J, Carlson L, Roland M, Stock P. Outcome of patients with HBV and HIV infections referred for liver transplantation. *Liver Transpl* 2006;12:801-7.
97. Stock P. Rapid deterioration of HIV coinfecting patients waiting for liver transplantation is not predicted by MELD. *Liver Transpl* 2005;11:1315-7.
98. Pache I, Duclos-Vallee JC, Teicher E, et al. Indications and timing for liver transplantation in HIV-coinfecting patients. *Hepatology* 2004;40(Suppl): A356.
99. Prieto M, Clemente G, Casafont F, et al. Documento de consenso de indicaciones de trasplante hepático. *Gastroenterol Hepatol* 2003;26:355-7.
100. Miró J, Torre-Cisneros J, Moreno A, et al. GESIDA/GESITRA-SEIMC, PNS and ONT Consensus Document solid organ transplant (SOT) in HIV-infected patients in Spain (March, 2005). *Enferm Infecc Microbiol Clin* 2005;23:353-62.