

Chapter 23: Management of ESLD in HIV coinfection

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Introduction

Liver disease due to chronic hepatitis B and C is currently one of the leading causes of morbidity and mortality among HIV-positive patients in the developed world. Non-coinfecting patients with chronic hepatitis C tend to progress to end-stage liver disease (ESLD) in 20-30 years, whereas coinfecting patients have higher rates of progression (Mohsen 2003; Poynard 2003). One meta-analysis demonstrated a higher overall adjusted relative risk (RR) of histological cirrhosis or decompensated liver disease in patients coinfecting with HIV and the hepatitis C virus (HCV) than in HCV-monoinfecting patients (Graham 2001). ESLD is common in coinfecting patients. We review different approaches to the condition.

Epidemiology

Of the approximately 40 million persons infected with HIV globally, 2 to 4 million are chronically infected with the hepatitis B virus (HBV) and 4 to 5 million have chronic HCV (Alter 2006).

The prevalence of HCV and/or HBV coinfection is high in developed countries. Studies performed in European HIV-positive patients showed rates of 33% and 9%, respectively (Rockstroh 2003; Konopnicki 2005), while in the USA figures are very similar, 28% and 9% (Fung 2004). Other authors have addressed the significance of HCV as a cause of non-AIDS-related death (Palella 2006; Crum 2006; Lewden 2005). One single-centre study (Martínez 2007) in Spain analysed the cause of 235 deaths in 4471 patients (5%) on combination antiretroviral therapy (cART) from 1997 until 2004. The number of patients who died from ESLD increased from 8% in 1997 to 41% in 2004, and in recent years this condition has become the leading cause of death in HIV-positive patients. In comparison with the general population of a similar age, deaths due to liver disease were 11 times more frequent in HIV-positive patients. Another prospective multicenter study (Rosenthal 2007) in France determined mortality due to ESLD in a nationwide population of HIV-positive patients. The authors followed a total of 20,940 HIV-positive patients, 4005 (19.9%) of whom were coinfecting, and showed that, in 2003, mortality due to ESLD represented 23.7% of non-AIDS-related deaths. In this population, ESLD was fatal in 1.5% of patients in 1995, 6.6% in 1997, 14.3% in 2001, and 12.6% in 2003, and 92.6% of patients who died from ESLD had chronic HCV infection. A prospective, observational study of 11 cohorts carried out in Europe, the United States and Australia included 23,441 HIV-1-infected patients (22.5% were HCV-positive) and followed them from December 1999 until February 2004. This study showed that, of the 1246 deaths recorded, those related to AIDS were the most frequent (31.1%), while liver disease was the most frequent non-AIDS-related cause (14.5%). HCV infection was shown to be an

independent predictor of liver-related death (D:A:D 2006). As for hepatocellular carcinoma (HCC), a recent study comparing liver-related deaths in HIV-positive patients (Salmon-Ceron 2009) described an increase in mortality due to HCC from 15% in 2000 to 25% in 2005 ($p=0.04$).

Clinical features of coinfecting patients with ESLD

One recent prospective study (Pineda 2009) that enrolled 154 patients with a new diagnosis of Child-Turcotte-Pugh class A compensated cirrhosis found that 36 patients (23.4%) developed a first hepatic decompensation during follow-up (mean 36 months). The probability of developing decompensated cirrhosis at 3 and 5 years was 26% and 33%, respectively. A multivariate analysis revealed that the factors predicting the emergence of an episode of hepatic decompensation at 5 years were Child-Turcotte-Pugh stage ($p=0.007$; HR, 3.33 [95% CI, 1.39-7.69]), lack of anti-HCV therapy ($p=0.035$; HR, 3.38 [95% CI, 1.14-5.04]), and baseline CD4 cell count below 300 cells/mm³ ($p=0.021$; HR, 2.40 [95% CI, 1.09-10.53]).

In a retrospective study, the same authors (Pineda 2005) described the frequency of specific events, such as the first decompensation and cause of death in HIV-negative and HIV/HCV-coinfecting subjects. Ascites and jaundice were more frequent among HIV-positive patients, while upper gastrointestinal bleeding and HCC were more frequent in mono-infected patients. Hepatic encephalopathy (HE) as both first decompensation and cause of death was higher in coinfecting patients.

The clinical characteristics and outcome of spontaneous bacterial peritonitis (SBP) were evaluated in an HIV-positive population with cirrhosis (Shaw 2006). Thirty-five HIV-positive patients with cirrhosis were compared with 70 HIV-negative patients with cirrhosis. An aetiological diagnosis was made in almost 80% of the HIV-positive cases and bacteraemia was present in more than 50%, with both rates being higher than those observed in HIV-negative patients. An important bacteriological finding in this study was the high incidence of *Streptococcus pneumoniae* as the aetiological agent of SBP among HIV-positive patients, second only to *Escherichia coli*.

HCC has a faster and worse outcome in HIV/HCV-coinfecting patients than in HCV-mono-infected patients (Puoti 2004; Bruno 2006).

The findings on HCC in 41 HIV-positive and 2384 HIV-negative patients were compared in an Italian study (Puoti 2004). The authors found a more aggressive course of HCC in HIV-positive patients, with an independent association between HIV infection and a more advanced stage of HCC at clinical presentation, in addition to a higher rate of infiltrating neoplasm and extrahepatic-extranodal metastasis. Furthermore, portal vein thrombosis was more frequent among HIV-positive patients with HCC.

A retrospective study from Canada and the USA compared 63 HIV-positive patients with HCC and 226 HIV-negative patients with HCC (Bräu 2007) and revealed that HIV+ patients were younger and more frequently symptomatic. In this cohort, median survival was similar between HIV-positive (6.9 months) and HIV-negative patients (7.5 months, $p=0.44$, log-rank), as was tumour stage.

Survival of HBV/HCV-mono-infected patients with HCC detected by screening has improved in recent years due to the advent of liver transplantation and radiofrequency ablation (RFA) (Chan 2008).

Prognosis after decompensation

The survival rate of HIV-positive patients with decompensated cirrhosis is much lower than that of HIV-negative patients—approximately 50% at 1 year of follow-up (Pineda 2005; Merchante 2006; Murillas 2009). In a multicentre case-control study (Pineda 2005), the outcome of cirrhosis after the first decompensation in coinfecting patients was much worse than in the monoinfected population. Survival at 1, 2, and 5 years for the coinfecting/monoinfected population was 54%/74%, 40%/61%, and 25%/44%, respectively. In another study (Merchante 2006) severity of liver disease (Child-Turcotte-Pugh score or HE as the first hepatic decompensation) and the level of cellular immunosuppression (< 100 CD4 cells) were identified as independent predictors of poor outcome in coinfecting patients. On the other hand, cART was associated with a reduced mortality rate.

Another study followed the outcome of 104 HIV-positive patients with HCC or cirrhosis after their first hepatic decompensation (Murillas 2009). The median survival time of this cohort was 14 months, similar to that observed by Merchante (13 months). This study included HCV and non-HCV-infected patients, and it did not find significant differences in survival based on the aetiology of cirrhosis, suggesting that HIV-positive patients have an overall poor outcome regardless of the nature of their liver disease. Furthermore, the MELD score and the inability to reach an undetectable plasma HIV-1 viral load at any time during follow-up were the only variables independently associated with the risk of death ($p < 0.001$). This is particularly relevant because recently the MELD score has been increasingly used to establish the prognosis of patients with cirrhosis and, consequently, to indicate liver transplantation.

Another recent prospective study (Girón-González 2007) that enrolled 92 HIV-positive patients with compensated and decompensated cirrhosis observed that the overall probability of death was 25% and 37% at 1 and 2 years, respectively. Independent factors associated with mortality due to liver cirrhosis were Child-Turcotte-Pugh score at inclusion, progression of this score at follow-up, more than one decompensation during follow-up, and absence of cART at follow-up.

HIV-positive patients with cirrhosis have a poor prognosis after the development of SBP (Shaw 2006). HIV infection was associated with a more than 6-fold increase in the probability of dying within a month of the first episode of SBP. Impaired renal function at diagnosis and severity of liver disease were identified as predictors of death. HIV-positive patients also had a dramatically shorter survival time than HIV-negative patients: only 50% of patients were still alive 3 months after the first episode of SBP and only 23% were alive after 1 year. Death was mostly related to complications of advanced liver disease rather than to AIDS-related conditions.

High mortality rates among coinfecting patients with ESLD waiting for liver transplantation have also been reported in observational studies (Maida 2005; Prieto 2008; Murillas 2009). In one study (Maida 2005), death due to ESLD occurred in 25% of patients during the evaluation period. Another study analysed 18 patients who were accepted for OLT and placed on the waiting list. Eight (44%) received a transplant, 8 (44%) died while on the waiting list, and 2 (12%) were still on the waiting list at the end of the study (Prieto 2008). 10 (67%) out of 15 patients on the transplant waiting list died after a median follow-up of 5 months, and 5 (33%) underwent liver transplantation (Murillas 2009).

Two case-control studies have analysed mortality rates among coinfecting patients with ESLD waiting for liver transplantation. In the first (Ragni 2005), mortality rates during the pre-transplant evaluation in HIV-positive (N=58) and HIV-negative (N=1359) patients were 36% and 15%, respectively ($p<0.001$), although these data were not confirmed by a recent American multicentre study (Subramanian 2009). Waiting list mortality was 14.4% in patients with HIV infection (N=167) and 11.1% in the control group (N=792) ($p=0.30$). In the multivariate analysis, a MELD score higher than 25 was the only variable related to death on the waiting list (Subramanian 2009).

A recent French study (Carmona 2009) identified factors associated with the mortality of HIV/HCV-coinfecting patients on the waiting list. The authors analysed different scores: MELD, MELD-Na, Child-Turcotte-Pugh, and ASA. Multivariate analysis showed that presence of cART at the time of the first referral ($p=0.04$), ASA score ($p=0.04$), and Child-Turcotte-Pugh score ($p=0.02$) were associated with mortality. The findings suggest that the Child-Turcotte-Pugh score rather than the MELD score should be used to predict mortality in these patients.

Physicians attending HIV-positive patients with cirrhosis should follow patients prospectively and evaluate them early for OLT after the first clinical decompensation of liver disease. Similarly, patients whose cirrhosis is associated with HCC should also be evaluated (Llovet 2004). Both prevention and effective treatment of these complications may improve the likelihood of survival until OLT, and this should be performed also with the HIV-negative patients (Agüero 2007; Merchante 2007).

Management of cirrhosis complications

Management of the complications of cirrhosis (portal hypertension, ascites, gastrointestinal bleeding, encephalopathy, SBP, HCC, and hepatorenal syndrome) must be planned, just as in the HIV-negative population (Cardenas 2005; Han 2006; Arroyo 2008). Medical management also includes prevention of infection. In view of the short survival associated with the development of SBP, primary antibiotic prophylaxis with quinolones or trimethoprim-sulfamethoxazole should be considered (Fernández 2007).

Another study (Pineda 2009) shows that transient elastometry could be used to select HIV/HCV-coinfecting patients undergoing screening with upper gastrointestinal endoscopy for oesophageal varices. This study found that HIV/HCV-coinfecting patients with cirrhosis who harbour oesophageal varices requiring preventive therapy for bleeding had liver stiffness values higher than those who did not require treatment. Liver stiffness values lower than 21 kPa were highly predictive of varices not at risk for bleeding.

As far as HCC is concerned, patients may benefit from more frequent imaging, i.e., every 3 months (Bräu 2007). Treatment of HCC may not be successful, depending on the stage. HCC is incurable in advanced stages.

In patients with hepatorenal syndrome, haemodialysis can be used as a bridge to liver transplantation; otherwise, it is usually fatal (Han 2006). The molecular adsorbent recirculating system (MARS) could be a new therapeutic tool in this setting, and may prove highly effective if combined with transplant/retransplantation (Gaspari 2006), although more evidence in coinfecting patients with ESLD and hepatorenal syndrome is needed.

Other issues that may delay the progression of liver disease, such as avoidance of hepatotoxic drugs (e.g., didanosine) and vaccination for hepatitis A and B, should be heeded.

Substance abuse

Smoking has been linked to HCC (Kuper 2000) and increased hepatic fibrosis (Pessione 2001) and it may also increase histological activity in chronic HCV patients irrespective of alcohol consumption (Hezode 2003).

According to one study (Rosenthal 2007), alcohol consumption was more frequent among coinfecting patients who died from ESLD (92%), and another study suggested that excess alcohol consumption increases HCV RNA levels (Cooper 2005).

In addition, a recent study found that daily cannabis smoking was significantly associated with the presence of moderate to severe fibrosis in patients with chronic HCV infection and recommend that those with hepatitis C cirrhosis should abstain from or reduce cannabis use (Ishida 2008).

HCV/HBV management

Specific treatment for infection with HBV or HCV is possible, although more difficult, in patients with advanced cirrhosis, especially for HCV infection (Soriano 2007; Rockstroh 2008).

One of the objectives when treating HCV-monoinfected patients with advanced liver cirrhosis using pegylated-interferon plus ribavirin is to obtain undetectable plasma HCV RNA levels at the time of OLT in order to reduce the risk of HCV recurrence post-transplant. One study (Everson 2005) using a low accelerating dosage regimen (LADR) of anti-HCV therapy in monoinfected patients on the OLT waiting list showed that 30 (24%) of 124 patients achieved a sustained virological response (SVR) and 12 (80%) of 15 patients who were HCV RNA-negative before OLT remained HCV RNA-negative 6 months or more after transplantation. This approach has not yet been addressed in coinfecting patients, although safety data can be extrapolated from the APRICOT sub-study (Mauss 2004). Hepatic decompensation was observed only in HIV/HCV-coinfecting patients with markers of advanced cirrhosis, and its incidence was 10.4% (14/134). However, 6 (43%) of the 14 patients died as a result of hepatic decompensation. One of the associated risk factors was antiretroviral treatment with didanosine. In contrast, no hepatic decompensation was noted in HIV/HCV-coinfecting patients without cirrhosis. Therefore, anti-HCV treatment during the pre-transplant evaluation or while patients are on the waiting list should be individualized (e.g., patients with Child-Turcotte-Pugh class A and HCC or genotypes 2/3) and patients must be monitored closely because of their high risk of hepatic decompensation and death.

According to the latest AASLD Practice Guidelines for HCV infection (Ghany 2009), HIV-infected patients with decompensated liver disease (CTP class B or C) should not be treated with peg-interferon + ribavirin, and should be considered candidates for liver transplantation (Grading IIa, C).

In a recent case-control study (Iacobellis 2007) comprising 129 HCV-monoinfected patients with decompensated cirrhosis, 66 were treated with peg-interferon plus ribavirin for 24 weeks and compared with the untreated control group (n=63). Thirteen patients discontinued treatment due to intolerance. SVR was observed in 82.6%, 43.5%, 30.2%, and 7% for HCV genotypes 2, 3, 1, and 4, respectively. In the treated group, the odds ratio for severe infection or death due to infection was higher, whereas ascites, encephalopathy, and oesophageal bleeding decreased. During follow-up, there were 15 deaths in the

controls and 9 in the non-responders. All patients who experienced SVR survived and did not need to undergo OLT. The authors concluded that HCV clearance via therapy is life-saving and reduces disease progression in HCV-monoinfected patients.

Since HBV replication is a contraindication for OLT and only patients without HBV viraemia are accepted for OLT, treatment of this infection should be a priority. HIV-positive patients who require antiretroviral therapy and have chronic HBV infection can be treated with lamivudine (or emtricitabine) and tenofovir as part of their triple antiretroviral therapy (Soriano 2007; GESIDA/PNS Panel of Experts 2009).

Adefovir and tenofovir have proven useful against HBV and could be used in cases of resistance to lamivudine (Soriano 2007).

Combination antiretroviral therapy (cART)

The role of cART in progression of liver disease and in overall mortality in HCV/HIV-coinfected patients remains controversial (Tedaldi 2003; Qurishi 2003). The use of protease inhibitors may offer protection from the progression of HCV-related fibrosis (Benhamou 2001; Macías 2006). Antiretroviral drug regimens should be carefully planned in persons with HIV and ESLD. These patients should follow general recommendations (GESIDA/PNS Panel of Experts 2009; Panel on Antiretroviral Guidelines for Adults and Adolescents 2009, Hammer 2008) and their liver function must be closely monitored for signs of hepatotoxicity. Careful consideration of drug prescriptions and possible interactions is essential.

Furthermore, some antiretroviral drugs may be contraindicated in cirrhotic patients (e.g., didanosine, nevirapine, full-dose ritonavir) and their dosing should be adjusted according to the degree of hepatic impairment (Wyles 2005; Back 2009; Tuset 2009).

Therapeutic drug monitoring (TDM) may be useful for efavirenz and protease inhibitors. Indinavir and atazanavir can increase unconjugated bilirubin levels by inhibiting UDP-glucuronosyltransferase. As total bilirubin is a component of both the Child-Turcotte-Pugh and MELD scores, results in patients taking these drugs should be interpreted with caution.

It is noteworthy that the new antiretroviral drug raltegravir, which is not a substrate of CYP450, can be used in HIV-1 OLT recipients. A recent French study (Tricot 2009) enrolled 13 patients with HIV-1 infection who underwent solid organ transplantation (8 liver and 5 kidney) and received raltegravir. The authors found a lack of significant interaction between raltegravir and calcineurin inhibitors that allowed simplified management of immunosuppressive treatment, excellent tolerability, and no events related to outcome (acute rejection) or HIV infection.

Finally, given the speed with which new antiretrovirals appear and thus new interactions, physicians should consult updated databases on drug interactions (Back 2009; Tuset 2009).

Orthopic liver transplant (OLT)

OLT is the only therapeutic option for patients with ESLD. HIV infection is not a contraindication for liver transplantation (Miro 2007; Stock 2007; Samuel 2008; Norris 2008). There are 3 different classes of criteria for including HIV-positive patients on the liver transplant waiting list: liver disease, HIV infection, and other criteria.

Liver disease criteria

These are the same as for the non-HIV-infected population; the main indication for OLT in HIV-positive patients is ESLD caused by HCV coinfection. Less frequent indications are HBV coinfection (either acute or ESLD) and liver cancer.

In the UK guidelines (O'Grady 2005), indications for liver transplantation include acute liver failure, decompensated liver disease—with ascites, encephalopathy (it is important to exclude HIV-related dementia), variceal bleeding that is difficult to manage with standard therapy, and poor liver function (albumin <30 g/l, INR >1.5, and elevated serum bilirubin >450 mmol/l)—and HCC detected during regular tumour surveillance. In the Eurotransplant region these criteria have been replaced by the MELD score. The criteria for liver transplantation in patients with HCC are as follows: no more than 3 tumour nodules, no nodule greater than 5 cm in diameter, absence of macroscopic portal vein invasion, and absence of recognizable extrahepatic disease.

A new indication for liver transplant in HIV+ patients has been described in a recent French study (Tateo 2009) in which 3 patients underwent liver transplantation and the cause of ESLD was nodular regenerative hyperplasia (NRH). OLT is the only therapeutic option in cases of severe portal hypertension such as that observed in these patients.

HIV infection criteria

Most liver transplant groups from Europe and North America use similar HIV criteria. These are summarized in Table 1 (O'Grady 2005; Grossi 2005; Miro 2007; Anonymous 2004).

	Spain [Miro 2005]	Italy [Grossi 2005]	UK [O'Grady 2005]	USA [Anon 2004]
Previous C events				
Opportunistic infections	Some*	None in the previous year	None after ART-induced immunological reconstitution	Some**
Neoplasms	No	No		No
CD4 cell count/mm³	>100***	>200 or >100 if decompensated cirrhosis	>200 or >100 if portal hypertension	>100***
Plasma HIV-1 RNA viral load BDL on HAART****	Yes	Yes	Yes	Yes

* In Spain, patients with previous tuberculosis, *Pneumocystis jiroveci* pneumonia (PCP) or esophageal candidiasis can be evaluated for OLT; ** In USA, PCP and esophageal candidiasis were not exclusion criteria; *** Patients with previous OIs should have >200 CD4 cells/mm³; **** If PVL was detectable, post-OLT suppression with cART should be predicted in all patients.

Table 1. HIV criteria for OLT in some European countries and the US.

Clinical criteria

Some authors are in favour of withdrawing exclusion criteria for some opportunistic infections that can be efficaciously treated and prevented, such as tuberculosis, candidiasis, and *Pneumocystis jiroveci* pneumonia (Roland 2003; Neff 2004; Radecke 2005). In fact, the NIH-sponsored study has recently updated the inclusion criteria for opportunistic complications and only untreated diseases are still an exclusion criteria for liver transplantation (e.g., progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, multidrug-resistant systemic fungal infections, primary CNS lymphoma, and visceral Kaposi's sarcoma) (Roland 2006).

Immunological criteria

All groups agree that the CD4+ lymphocyte count should be above 100 cells/mm³ for OLT (Roland 2003; Neff 2004). This figure is lower than that for kidney transplantation (CD4 >200 cells/mm³), because patients with cirrhosis often have lymphopenia due to hypersplenism, which leads to a lower absolute CD4+ count, despite high CD4 percentages and good virologic control of HIV. In Spain and the USA, the CD4+ count must be greater than 200 cells/mm³ in patients with previous opportunistic infections (Miro 2005; Anonymous 2004).

In Italy (Grossi 2005) and the UK (O'Grady 2005) the CD4+ cut-off is 200 cells/mm³, unless patients have decompensated cirrhosis or portal hypertension. In these scenarios, they use the same CD4+ cell threshold as in Spain and the USA (100 cells/mm³).

Virological criteria

The essential criterion for OLT is that the patient must be able to have effective, safe and long-lasting cART during the post-transplant period (Neff 2004; Fung 2003). The ideal situation is one in which the patient tolerates cART before transplant and is ready for the transplant with undetectable HIV viral load by ultra-sensitive techniques (<50 copies/ml). Some patients do not have an indication for cART, as they are long-term non-progressors with no immunological criteria (CD4+ lymphocyte count above 350 cells/mm³) or clinical criteria to start cART and a detectable plasma viral load. In this setting, it is unknown whether and when (pre-transplant or post-transplant) it would be beneficial to initiate cART in order to reach an undetectable plasma viral load.

Other criteria

To be included on the OLT waiting list, an HIV-infected patient must have a favourable psychiatric evaluation. One recent observational prospective study found that ESLD patients with HIV-1 infection improved on all the items of a psychometric score (MADRS) at the follow-up evaluation (Barbanti 2009). In this study, the score variation was 10.20 at baseline and 4.09 at follow-up (p<0.001).

Patients who actively consume drugs should not be placed on the waiting list. In Spain, patients must have undergone a 2-year consumption-free period for heroin and cocaine (Miro 2005), and 6 months with no consumption of other drugs (e.g., alcohol). Patients who are on stable methadone maintenance programmes can be included and can continue on the maintenance programme after the procedure (Liu 2003). Fi-

nally, as is the case with any transplant candidate, HIV-positive patients must show an appropriate degree of social stability in order to ensure adequate care in the post-transplant period.

Outcome of OLT in HIV-positive patients

Overall short-term survival rates of HIV-positive patients who undergo OLT have been reported to be similar to those of HIV-negative patients when there is no HCV coinfection (Fung 2004; Roland 2002; Ragni 2003; Neff 2003; Norris 2004; Duclos-Vallée 2006; De Vera 2006; Schreiber 2007; Coffin 2007; Grossi 2008; Tateo 2009) (Table 2).

Author	Year	Country	N° cases	Virus	Follow-up (months)	Survival rate
Roland	2002	International	19	Most HCV	10	15 (79%)
Ragni	2003	International	24	HCV, 62% HBV, 29%	17	18 (75%)
Neff	2003	US	16	HCV or HVB	12	14 (87%)
Fung	2004	US	29	HCV, 90%	18	20 (69%)
Norris	2004	UK	14	HCV, 50% HBV/OH, 50%	12 19	2 (29%) 7 (100%)
Duclos-Vallée	2006	France	41	HCV, 88% HBV, 12%	18	29 (81%) 5 (100%)
De Vera	2006	US	27	HCV, 100%	27	13 (48%)
Schreiber	2007	US	15	HCV, 40% HBV, 33%	74	10 (67%)
Coffin	2007	US	16	HBV 100%	8.5	14(86%)
Grossi	2008	Italy	60	HCV 65% HBV 12%	12	41 (58.3%)
Tateo	2009	France	13	HBV 100%	32	13 (100%)
Spanish study*	2010	Spain	200	HCV, 96%	35	57 (71.5%)

Table 2. Liver transplantation in HIV infected patients: main cohorts of cases (≥10) in the late cART era (2002-2009).

HIV-positive patients have not been shown to have an increased risk of post-operative complications or a higher incidence of opportunistic infections or tumours than HIV-negative patients (Samuel 2008; Norris 2008). Although findings from a recent case-control study (81 HIV/HCV-coinfected liver transplant recipients vs. 213 control patients) found that coinfecting individuals were about twice as likely to have treated acute rejection than HCV-monoinfected patients (35% vs 18%, $p=0.001$) (Terrault, 2009). Bacterial infections were common in liver (43%) and kidney recipients (35%), and HCV infection was the only factor associated with an increased risk of bacterial

infection (liver recipients only) (Blumberg 2008). A recent study (Moreno 2009) that included 84 HIV/HCV-coinfected patients who underwent liver transplantation found bacterial infections in 39 patients (46%), CMV infection in 21 (25%), Herpes virus infection in 13 (15%), and fungal infections in 14 patients (17%) (5 were invasive cases). Fungal infection was associated with death ($p=0.01$).

HIV/HCV Coinfection

Mid-term survival is affected by recurrent hepatitis C (De Vera 2006). After OLT, recurrence of HCV infection is universal, regardless of whether the patient is infected by HIV or not. In fact, it is currently the number one cause of death. Some studies have suggested that recurrence of HCV in coinfecting patients tends to be more severe and occurs earlier (De Vera 2006; Castells 2006). A recent French study (Antonini 2009) that included 68 HIV/HCV-coinfected patients who underwent OLT found that 19% of recipients developed cirrhosis and 13% developed fibrosing cholestatic hepatitis with a mean delay of 18.9 months and 6 months, respectively.

One study compared the outcomes of 27 coinfecting patients with 54 HCV-monoinfected patients who underwent OLT (De Vera 2006). The researchers found that HIV-positive patients had a higher likelihood of developing cirrhosis or dying of an HCV-related complication than HIV-negative patients ($RR = 2.6$; 95%CI, 1.06-6.35; $p=0.03$). Cumulative 1-, 3- and 5-year survival for coinfecting and monoinfected patients was 67% vs. 76%, 56% vs. 72%, and 33% vs. 72%, respectively ($p=0.07$).

In a recent retrospective study (Mindikoglu 2008) in the USA that enrolled 138 HIV-positive patients who underwent liver transplant during the cART era (1996-2006), the rate of survival at years 2 and 3 was significantly lower in HIV-positive patients (70% and 60%) than in the general population ($n=30,520$) (81% and 77%), although this difference was observed only in the HCV/HIV-HBV/HIV coinfecting group. None of the 24 HIV-monoinfected recipients died. Therefore, liver transplant in HIV-positive patients does not have higher short-term mortality (1-2 years). Nevertheless, the management and outcome of HCV reinfection could affect survival in the medium term (3-5 years) and long term (5-7 years).

In France, data from 35 HIV/HCV-coinfected patients were analysed and compared with those of 44 HCV-monoinfected patients. The rates of survival at 2 and 5 years were 81%/91% and 51%/73% in HIV/HCV-coinfected patients/HCV-monoinfected patients, respectively ($p=0.004$) (Duclos-Vallée 2008).

In Spain, data from a multicentre case-control study show that survival of HIV/HCV-coinfected patients ($N=84$) at 1 year was similar to that of HCV-monoinfected patients ($N=252$)—88% vs. 89% (NS)—but it was significantly lower at 3 and 5 years: 62% vs. 77% and 48% vs. 75%, respectively ($p<0.01$). In multivariate analysis, the variables independently associated with mortality were HCV genotype 1 infection, non-traumatic donor death, number of units of blood transfused during surgery, and development of invasive fungal infection after transplant (Miró 2009). The role of HCV infection is also well demonstrated in another recent case-control study performed in the UK that included 33 HIV-infected patients (0.6% of total LT activity), 847 HCV-monoinfected patients (15% of LT activity), and 5435 HIV-negative patients (Joshi 2009). Compared with the HCV group, survival rates at 1 year and 5 years differed significantly

in the HIV-positive patients (73% and 53% [HIV-positive/HCV] vs. 100% and 100% [HIV-positive/other] vs. 87% and 69% [HCV], log-rank test, $p=0.04$). No difference in survival rates at 1 and 5 years was demonstrated between the HIV-negative and HIV-positive groups (86.5% and 74% vs. 87.1% and 78%, log-rank test, $p=NS$). However, a recent Italian case-control study (Baccarani 2009) that included 27 HIV-positive and 24 HIV-negative recipients found that patient and graft survival at 1, 2, and 4 years were 90%, 82.5%, and 82.5% for HIV-positive patients vs. 100%, 94%, and 79% for HIV-negative patients ($p=0.64$), and 95%, 87%, and 87% for HIV-positive patients vs. 95%, 89%, and 82% for HIV-negative patients ($p=0.89$), respectively. However, the median follow-up was only 21 months (range 2-47) and 29 months (range 3-39) for HIV-positive recipients and HIV-negative recipients ($p=0.93$), respectively, and the aetiology of ESLD was HCV in most cases (70% vs. 61% respectively).

However, additional cohort studies analysing donor and recipient characteristics and issues related to the activity of both viruses and the efficacy and safety of antiviral therapies are necessary in order to determine the long-term prognosis of this procedure.

Rapid progression of HCV-related liver disease in HIV-positive recipients would represent a major drawback and would shorten life expectancy in this group. In fact, it is currently the number one cause of death. A French study observed that progression to fibrosis ($\geq F2$) was significantly higher in HIV-positive patients ($p<0.0001$) (Duclos-Vallée 2008) and MELD was the only significant predictor of mortality, although donor age was of borderline significance ($p=0.06$).

Other negative survival factors reported by a multicentre Spanish study were histological progression to cirrhosis (F4) and donor age (Miro 2008).

Author, Year of Publication	HIV/HCV coinfecting patients		Non-HIV HCV monoinfected patients (Control Group)	
	No. of cases	SVRa No (%)	No. of cases	SVRa No (%)
Fung, 2004	12	2 (17%)	-	-
Duclos-Vallee, 2006	13	2 (15%)	-	-
de Vera, 2006b	15	4 (27%)	27	7 (28%) ^c
Vennarecci, 2006d	9	0 (0%)	-	-
Castells, 2007e	5	1 (20%)	9	1 (11%)
Spanish study, 2009	41	9 ^f (22%)	-	-
Total	90	17 (18.8%)	-	-

aSVR: sustained virological response; bMost cases were genotype 1. Three patients were treated with classical interferon plus ribavirin; cRate of sustained virological response was not specified. Data show the rate of virologic response (clearance of HCV RNA from serum); d The authors did not specify the type of interferon used; and, eThese patients were included in the Spanish study and were not taken into account for the overall response rate. f 3/27 (11%) Genotype 1-4 and 6/13 (46%) genotype 2-3. Modified from Miro et al. J HIV ther. 2007; 12(1):24-35.

Table 3. Summary of the studies evaluating the effectiveness of the treatment of HCV re-infection in OLT with pegylated-interferon + ribavirin.

There is insufficient experience on the efficacy and safety of therapy with pegylated-interferon and ribavirin in coinfecting transplant patients. One study (Miró 2007) summarized the reports evaluating the effectiveness of treatment of HCV reinfection in OLT with pegylated-interferon + ribavirin (Fung 2004; Duclos-Vallée 2008; De Vera 2006; Vennarecci 2006; Castells 2007; Miró 2009). These patients were treated when they had histological criteria. Only 12 (18.5%) out of 65 HCV/HIV-coinfecting patients achieved an SVR. Krishnan et al (2008) investigated SVR-associated factors in 23 HIV/HCV-coinfecting liver recipients and found (using logistic regression analysis) that donor age <60 years ($p=0.02$), genotype other than 1 ($p=0.001$), and use of cyclosporin A ($p=0.002$) were independently correlated with SVR. New strategies are necessary to improve the outcome of HCV recurrence in this setting. In this sense, a recent German study showed that SVR was obtained in the 6 out of 7 patients treated within the first 3 months after OLT (Emmelkamp 2007). Finally, a recent study has described 2 cases of spontaneous clearance of HCV RNA after OLT. This phenomenon is very infrequent and its mechanism is not known (Bhagat 2008).

On the other hand, in two recent genome-wide association studies (Ge 2009; Thomas 2009), a single nucleotide polymorphism (rs12979860) 3 kilobases upstream of the IL28B gene, which encodes the type III interferon- λ , was shown to be associated with natural clearance of HCV among HIV-negative individuals of both European and African ancestry and with more than a twofold difference in response to anti-HCV drug treatment with pegylated-interferon and ribavirin in HCV mono-infected patients. In a Swiss study (Rauch 2010), this antiviral effect was stronger in patients with HCV genotypes 1 or 4. Similar results have been recently communicated in HCV/HIV coinfecting patients (Rallon 2010). The role of IL28B polymorphisms of the donor and their impact on the natural history of HCV recurrence and response to antiviral therapy in liver transplant recipients is not yet understood.

HIV/HBV coinfection

Cohorts of HIV/HBV-coinfecting patients are not as large as those of HIV/HCV-infected patients. Nevertheless, the outcome of HBV infection after OLT is much better (Terrault 2006; Coffin 2007; Grossi 2008; Joshi 2009; Tateo 2009). The survival rate in the short and medium term in HBV/HIV-coinfecting patients is high and similar to that observed in HBV-monoinfected patients, probably due to the low incidence of HBV reinfection. A recent French study (Tateo 2009) that included 13 HIV/HBV-coinfecting patients (3 out of 6 patients with positive anti-HCV serology had HCV RNA detectable before OLT), revealed 100% graft and patient survival after a mean follow-up of 32 months. Another recent study (Joshi 2009) described a 5-year survival rate of 100% in 6 HIV/HBsAg-positive patients. The presence of HBV resistance to lamivudine at the time of transplantation was a potential risk for recurrence of HBV after OLT (Terrault 2006).

Hepatocellular carcinoma

Preliminary Italian experience showed good results in 7 HIV-1-infected patients with HCC who underwent OLT. They observed an 86% overall patient and graft survival rate after a mean follow-up of 8 months, and recommend OLT in HIV-positive pa-

tients with early stage HCC (Di Benedetto 2006; Di Benedetto 2008). A recent Italian study found no recurrence in 7 HIV-1 OLT recipients after a median follow-up of 13 months (Di Benedetto 2008).

A French study (Vibert 2009) compared the histological characteristics of HCC in the explanted liver from 21 HIV/HCV-coinfected recipients and 53 HCV-monoinfected recipients who underwent OLT due to HCC. For pathologically confirmed HCC, no significant differences between HIV-positive patients and non-HIV-infected patients were noted for the number of nodules (2.0 vs. 3.1, $p=0.23$), the maximum diameter of nodules (30 mm vs. 29 mm, $p=0.88$), the sum of nodule diameters (45 mm vs. 54 mm, $p=0.46$), presence of satellite nodules (8/15 vs 24/53, $p=0.69$), microvascular invasion (7/15 vs 22/53, $p=0.3$), mean tumour necrosis (35% vs 42%, $p=0.50$), and Edmonson grade (2.9 vs 2.8, $p=0.56$). Another French study (Vibert 2008) compared HIV-positive and HIV-negative patients with HCC. They found that the proportion of excess Milan criteria were similar (2/20 [19%] vs. 11/61 [18%]). The time on the waiting list was similar (7 vs. 4 months). Thirteen HIV-1-infected patients and 55 HIV-negative patients had a transplant. The pathological findings were similar in both groups for number of nodules (2.3 vs. 2.6, $p=0.70$), maximum diameter (27 mm vs. 28 mm $p=0.82$), satellite nodules (4/13 vs. 21/49, $p=0.39$), and vascular invasion (6/13 vs. 22/48, $p=0.98$). It is noteworthy that the Edmonson grade was higher in HIV-positive patients (3.1 vs. 2.5, $p=0.04$). After a mean follow-up of 16 months and 24 months ($p=0.11$) tumour recurrence was observed in 4/13 (30%) vs. 2/49 (4%) OLT recipients, respectively. This is the only study to have noted such a high recurrence rate. Further studies with a higher number of cases and longer follow-up are needed in order to know the efficacy of OLT in HIV-1-positive recipients with HCC.

Conclusions

ESLD is an increasingly frequent clinical scenario in the setting of HIV/HCV coinfection, and its relevance has grown since cART became available.

Early diagnosis of ESLD complications is particularly important and should be actively monitored and treated. In general terms, the management of ESLD in HIV-positive patients should be the same as in those without HIV infection.

Physicians attending ESLD patients should follow them prospectively and evaluate them for OLT after the first clinical decompensation of the liver disease.

OLT is a life-saving procedure in this population, and is safe and effective in patients with HBV infection. However, recurrence of HCV infection in coinfecting patients can affect both graft and patient survival in the medium and long term. Prospective and larger studies with a longer duration must be carried out to determine the benefit of OLT in this setting.

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