Adult Liver Transplantation in HIV-1 Infected Patients

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Abstract

The prognosis of HIV infection has dramatically improved in recent years with the introduction of combined antiretroviral therapy. Currently, liver disease is one of the most important causes of morbidity and mortality, even more so given the high rate of hepatitis C virus coinfection in countries where drug abuse has been an important HIV risk factor. Survival of HIV-coinfected patients with end-stage liver disease is poor and shorter than that of the non HIV-infected population. One-year survival of HIV-infected patients with end-stage liver disease is only around 50-55%. Infection with HIV is no longer a contraindication to transplantation, which is becoming a standard therapy in most developed countries. The HIV criteria used to select HIV-infected patients for liver transplantation are quite similar in Europe and North America. Current criteria state that having had an opportunistic infection (e.g. tuberculosis, candidiasis, Pneumocystis jiroveci pneumonia) is not a strict exclusion criterion. However, patients must have a CD4 count above 100 cells/mm³ and a plasma HIV-1 RNA viral load which is suppressible with antiretroviral treatment. More than 300 orthotopic liver transplants in HIV-infected patients have been published in recent years and the mid-term (three-year) survival was similar to that of HIV-negative patients. The main problems in the posttransplant period are the pharmacokinetic and pharmacodynamic interactions between antiretroviral and immunosuppressive agents and the recurrence of HCV infection, which is the principal cause of posttransplant mortality. There are controversial results regarding mid-term survival of HIV/HCV-coinfected patients in comparison with HCV-monoinfected ones. However, one study showed a trend of poorer five-year survival of HIV/HCV-coinfected patients. There is little experience with the treatment of recurrent HCV infection. Preliminary studies showed rates of sustained virologic response ranging between 15-20% in HIV/HCV-coinfected recipients. Liver transplantation in HIV/HBV-coinfected patients had a good prognosis because HBV recurrence can be successfully prevented using immunoglobulins and anti-HBV drugs. Finally, this field is evolving continuously and the indications for liver transplantation or the management of HCV coinfection may change in the future as more evidence becomes available. (Trends in Transplant. 2008;2:78-91)

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Key words

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Introduction

The rate of HIV-related mortality has declined dramatically since 1996 in Europe and the USA with the widespread use of combined antiretroviral therapy (cART). Conversely, end-stage liver disease (ESLD), mainly caused by hepatitis C virus (HCV), is becoming an important cause of death among human immunodeficiency virus-1 (HIV-1)-infected patients[1-4]. Orthotopic liver transplantation (OLT) is the only therapeutic option for patients with ESLD[5,6]. However, until a few years ago, infection with HIV was an absolute contraindication to any type of transplantation. The prognosis and the fear that transplant-associated immunosuppression could speed up the progression to AIDS or increase the risk of opportunistic infections meant that OLT was ruled out[7]. The spectacular improvement in prognosis observed in HIV-infected patients after the introduction of cART in 1996 has meant that transplantation has now been reconsidered in patients with ESLD. The main objective of this paper is to define the criteria to select HIV-infected patients for OLT, taking into account that this field is evolving continuously and the indications for OLT or management of these patients may change as more evidence becomes available.

Experience of orthotopic liver transplantation in HIV infected patients in the combined antiretroviral therapy period (1996-2006)

Initial attempts at OLT in HIV-infected patients before the introduction of cART regimens (before 1996) provided very poor results. Putting together the most important case series published[8-10], three-year survival was only 44%. Most patients died because of HIV-disease progression, with graft function being normal in many cases. However, since the introduction of cART in 1996, HIV-infected recipients of liver transplants have improved their short- and mid-term survival. Accumulated experience in North America and Europe in the last 10 years has shown that more than 300 OLT cases were performed[11-20] (Table 1). Survival was greater than 70% in most series with different periods of follow-up. In more than two-thirds of cases, the primary indication for OLT was HCV coinfection. Although cases came from different institutions, the criteria used for liver transplantation were quite similar. In general, candidates did not have a prior history of opportunistic infections, and had CD4 counts > 100 cells/µl and undetectable plasma HIV RNA on cART (or available drugs for successful treatment in the post-OLT period)[14,21]. In a multicentre and multinational retrospective study performed by Ragni, et al., including 23 HIV-infected patients who underwent OLT, survival at three years was 73 and 79% (p = NS) for HIV-infected and non HIV-infected recipients, respectively[12]. Similar rates were seen for graft survival. In all cases published in the cART era, the main cause of death was due to hepatitis C recurrence. In any case, three-year survival in HIV-infected recipients in the cART period was almost 30% higher than in the pre-HAART era[8-10] and therefore, at present, HIV infection is no longer a formal contraindication to transplantation. However, de Vera, et al.[17] recently published one single-center series of HIV/HCV-coinfected patients with the longest mean follow-up (27 ± 5 months). They did a case-control study comparing the evolution of 27 HIV/HCV-coin-

Table 1. Liver transplantation in HIV-infected patients: main series of cases (≥ 10) in the late combined antiretroviral therapy era (2002-2008)

Author	Year	Country	No. cases	Virus	Follow-up (months)	Survival rate
Roland, et al.[11]	2002	Internacional	19	Most HCV	10	15 (79%)
Ragni, et al.[12]	2003	Internacional	24	HCV 62% HBV 29%	17	18 (75%)
Neff, et al.[13]	2003	USA	16	HCV or HBV	12	14 (87%)
Fung, et al.[14]	2004	USA	29	HCV 90%	18	20 (69%)
Norris, et al.[15]	2004	U.K.	14	HCV 50% HBV/OH 50%	12 19	2 (29%) 7 (100%)
Duclos-Vallée, et al.[16]	2006	France	41	HCV 88% HBV 12%	18	29 (81%) 5 (100%)
De Vera, et al.[17]	2006	USA	27	HCV 100%	27	13 (48%)
Schereibman, et al.[18]	2007	USA	15	HCV 40% HBV 33%	74	10 (67%)
Coffin, et al.[19]	2007	USA	16	HBV 100%	8,5	14(86%)
Spanish study*	2008	Spain	127	HCV 94%	21	89(74%)
Grossi, et al.[20]	2008	Italy	60	HCV 65% HBV 12%	12	41(58.3%)

*Unpublished data.

fected patients with 54 HCV-monoinfected patients (control group) who underwent OLT. Five-year survival was poorer in coinfected patients (33 vs. 72%), although this difference was not statistically significant (p = 0.07). In a recent retrospective study carried out in the USA that enrolled 138 HIV-infected patients with liver transplant in the cART era (1996-2006), the rate of survival at two and three years was significantly lower in the patients with HIV infection (70 and 60%) than in the general population (81 and 77%; n = 30,520), although this difference was observed in the HCV/HIV and HBV/HIV-coinfected group exclusively. None of the 24 transplanted HIV-monoinfected patients died. Therefore, liver transplantation in HIV-infected patients does not have a higher short-term mortality (1-2 years). Nevertheless, the management and outcome of HCV reinfection could affect the survival in the medium (3-5 years) and long term (5-7 years)[22].

In France, Duclos-Vallee, et al. analyzed the data of 35 HIV/HCV-coinfected patients and compared them with 44 HCV-monoinfected patients. The rates of survival at two and five years were 81 and 91% in HIV/HCV-coinfected patients and 51 and 73% in HCV-monoinfected patients, respectively (p = 0.004)[23].

Conversely, in a Spanish multicentre case-control study[24], the survival rate of patients and grafts at three years was similar in HIV/HCV-coinfected patients (n = 51) to that in HCV-monoinfected patients (n = 1,177). The survival rates at one, two, and three years were 88 versus 81%, 75 versus 74%, and 64 versus 69%, respectively (p = NS). Although there are no available data at five years in this Spanish study, the differences observed between the Spanish results and the French and American ones show the real need to implement multicentre studies with high number of cases, which may allow examining the different factors that could have an influence in the long-term prognosis of this procedure and to explain these differences. Variables like donor and recipient characteristics, viral kinetic of both viruses, and the efficacy and safety of antiviral

Table 2. HIV criteria for orthotopic liver transplantation in some European countries and the USA

	Spain[30]	Italy[34]	UK[29]	USA[35]
Previous C events:				
Opportunistic infections	Some*	None in the previous year.	None after HAART-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

BDL: Below detections levels (< 200 copies/ml).
*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 exclusión criteria.
‡Patients with previous opportunistic infections should have > 200 CD4 cells/mm³.
§If PVL was detectable, post-OLT suppression with combined antiretroviral therapy should be predicted in all patients.

therapy could have an impact on the outcome of these patients and, therefore, they must be analyzed.

In Spain, the OLT program in HIV-infected patients, started in January 2002 (GESIDA unpublished data), has performed 127 liver transplants in 122 patients up to March 2008. More than 95% of patients were HCV/HIV-coinfected. There were 33 deaths (26%) after a median follow-up of 21 months.

Magnitude of end-stage liver disease in Europe and the USA

According to current estimates, there are around 540,000 HIV-infected patients in Western European countries[25].

The prevalence of HCV and HBV coinfection in European HIV-infected patients was 33 and 9%, respectively[26,27]. Thus, the estimated number of HCV-and HBV-coinfected patients is around 180,000 and 49,000 cases, respectively. In a cross-sectional study performed in Spain[28], 8% of coinfected patients had clinical or histological criteria of cirrhosis and 17% of them met the Spanish criteria to be admitted in an OLT waiting list. Therefore, the potential number of candidates for OLT in Europe would be around 3,100 cases.

According to these studies[25,28], in Spain there are 77,000 HCV-coinfected individuals and 7,000 HBV-coinfected patients among a total number of 140,000 HIV-infected patients.

Using the same calculations, the potential number of candidates to be evaluated for liver transplantation would be around 1,142 cases.

Criteria for including HIV-infected patients in the liver transplant waiting list
Liver disease criteria

Criteria concerning the liver disease are the same as for the non HIV-infected population, the main indication for OLT in HIV-infected patients being ESLD caused by HCV coinfection. Less frequent indications were HBV coinfection (either acute or ESLD) and liver cancer. The British HIV Association, with the UK and Ireland Liver Transplantation Center, has recently published a Consensus Guideline reviewing the liver disease criteria as well as the HIV-infection criteria[29].

In this guide, indications for liver transplantation include acute liver failure, decompensated liver disease (with ascites, encephalopathy [it is important to exclude HIV-related dementia], or variceal bleeding difficult to manage with standard therapies, and poor liver function [e.g. albumin < 30 g/l, INR > 41.5 and elevated serum

bilirubin > 450 mmol/l]) and hepatocellular carcinoma (HCC) detected during regular tumor surveillance. Criteria for liver transplantation in patients with HCC are: no more than three tumor nodules, no nodule must be > 5 cm in diameter, absence of macroscopic portal vein invasion, and absence of recognizable extrahepatic disease[29].

HIV-infection criteria in Spain

In Spain, a multidisciplinary Task Force[30] has defined the following clinical, immunologic, and virologic criteria.

Clinical criteria

Ideally, patients should not have suffered previously from AIDS-defining diseases, as they may have a greater risk of reactivation. However, the improved prognosis post-cART means that some authors are in favor of withdrawing exclusion criteria for some opportunistic infections which can be efficaciously treated and prevented, such as tuberculosis, candidiasis, and *Pneumocystis jirovecii* pneumonia[21,31-33].

The Spanish Task Force considered that the experience with other HIV-related opportunistic infections and tumors (e.g. Kaposi sarcoma) is still too limited to make any recommendations.

Immunologic criteria

All groups have agreed that the CD4+ lymphocyte count should be > 100 cells/mm^3 for OLT[34,35].

This figure is lower than that used for kidney transplantation (i.e. CD4 > 200 cells/mm^3) 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.

Virologic criteria

The essential criterion for OLT is that the patient must be able to have effective and long-lasting antiretroviral therapy during the posttransplant period[30]. The ideal situation is one in which the patient tolerates cART before transplantation and is ready for the transplant with undetectable plasma HIV viral load by ultrasensitive techniques (< 50 copies/ml). Nevertheless, this is not always possible for several reasons:

1. In some patients with ESLD it may be difficult to maintain an undetectable HIV viral load in plasma because they often experience intolerance or toxicity related to antiretroviral drugs, which must then be stopped. In these cases, and to avoid resistance, it is better to save antiretroviral therapy for the posttransplant period.

2. Some patients remain viremic with cART. In these cases, it is mandatory to carry out antiretroviral sensitivity testing (genotypic or phenotypic resistance testing)[36] to ascertain the real therapeutic options. The evaluating team and HIV experts will evaluate whether the patient has effective and durable rescue therapy.

3. Some patients do not have an indication for cART as they are long-term nonprogressors or do not have immunologic criteria (CD4+ lymphocyte count > 350 cells/mm^3) or clinical criteria to start cART and, therefore, they have viremia that is detectable in plasma. In this setting, it is unknown whether and when (pretransplant or posttransplant) it would be beneficial to initiate cART in order to reach an undetectable HIV viral load in plasma.

Other criteria

Furthermore, to include an HIV-infected patient on the OLT waiting list, the candidate must have a favorable psychiatric evaluation. Patients who actively consume drugs will be excluded. In Spain, it is recommended that there be a consumption-free period of two years for heroin and cocaine[30] and six months without addiction for other drugs (e.g. alcohol). Patients who are on stable methadone maintenance programs are not excluded from transplantation and can continue on such programs after the transplant[37].

Finally, as is the case with any transplant candidate, HIV-infected patients must show an appropriate degree of social stability to ensure an adequate care in the posttransplant period.

HIV criteria in other European and North America countries

Most liver transplant groups from Europe and North America are using similar HIV criteria, which are summarized in table 2[29,30,34,35]. It is important to point out that, currently, to have a previous opportunistic infection is not a strict exclusion criterion by itself. In fact, the NIH-sponsored study has recently updated the inclusion criteria for opportunistic complications[38] and only those diseases without therapy remain exclusion criteria for liver transplantation (e.g. progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, multidrug-resistant systemic fungal infections, primary central nervous system lymphoma, and visceral Kaposi's sarcoma). On the other hand, a CD4 cell count > 200 cells/mm^3 is the cutoff used in Italy[34] and the UK[29], unless patients had decompensated cirrhosis or portal hypertension, respectively. In these scenarios, they use the same CD4 cell threshold used in Spain and the USA (e.g. 100 cells/mm^3)[30,35].

Special considerations in HIV-infected patients

Orthotopic liver transplantation in HIV-infected patients is a complex scenario that requires a multidisciplinary approach[6,21]. Sites wishing to carry out transplants in HIV-positive patients must have a multidisciplinary team that can periodically evaluate these patients during the pre- and posttransplant periods. The team should include members from the liver transplant team (medical and surgical), infectious diseases and HIV specialists, a psychologist/psychiatrist, an expert on alcoholism and drug abuse, and a social worker.

Controversial issues in the pretransplant period

Waiting list mortality in HIV-infected patients with ESLD is very high. This is because survival of HIV-infected patients with decompensated cirrhosis is much lower than in HIV-negative patients[39-41]. Pineda, et al.[40] have recently shown in a multicentre case-control study performed in Andalusia (Spain) that the outcome of cirrhosis after the first decompensation in HIV/HCV-coinfected patients is much worse than in the HCV-monoinfected population. Survival at one, two, and five years for coinfected and monoinfected populations was 54/74%, 40/61% and 25/44%, respectively. In another study[41], the same group of investigators identified as independent predictors of a poor outcome in HIV/HCV-coinfected patients the severity of liver disease (Child-Turcotte-Pugh [CTP] classification or developing hepatic encephalopathy as the first hepatic decompensation) and the level of cellular immunosuppression (< 100 CD4 cells/mm^3). On the other hand, HAART was associated with a reduced mortality.

Another Spanish study has followed the evolution of 104 HIV-infected patients with cirrhosis after their first hepatic decompensation or HCC[39]. Median survival time of this cohort was 14 months, similar to the Merchante's cohort (13 months)[40]. This study included HCV-infected and non HCV-infected patients and we did not find significant differences in survival according to the etiology of cirrhosis, suggesting that HIV-infected patients have an overall poor outcome regardless of the nature of their liver disease. Furthermore, the model for end-stage liver disease (MELD) score was the only factor independently associated with mortality. This is of relevance because during the last years MELD has been increasingly used to establish the prognosis of patients with cirrhosis and, consequently, to indicate liver transplantation.

Once the HIV-infected patient with ESLD is included in the transplant waiting list, mortality of HIV-infected patients remained very high (> 60%). This occurred mainly because, in most Spanish centers, prioritization for organ allocation was predominantly established on the basis of the time in the waiting list. In comparison, the annual mortality rate for non HIV-1-infected patients while on the liver transplant waiting list in

our center ranged between 8-12% in recent years. High mortality rates of HIV/HCV-infected patients with ESLD waiting for liver transplantation have been previously reported in two studies[42,43]. In one of these studies[43], mortality rates during pretransplant evaluation among HIV-positive (n = 58) and HIV-negative (n = 1,359) patients were 36 and 15%, respectively (p < 0.001).

Nevertheless, these data have not been verified in a recent U.S. multicentre study. Mortality in the waiting list was 14% in patients with HIV infection (n = 167) and 11% 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 in the waiting list[44].

In any case, physicians attending cirrhotic HIV-infected patients should prospectively follow these patients and they should evaluate them early for OLT after the first clinical decompensation of the liver disease: ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, gastroesophageal variceal bleeding and/or jaundice. Similarly, patients whose cirrhosis is associated with HCC should also be evaluated. Both prevention and effective treatment of these complications may improve the likelihood of patient survival until OLT[45-48].

Regarding the antiretroviral therapy, these patients should follow the general recommendations[49,50] and their liver function must be closely monitored in order to detect hepatotoxicity. 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[51-53]. Therapeutic drug monitoring 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 CTP and MELD scores, their results in patients taking these drugs should be interpreted cautiously.

On the other hand, organ transplantation in HIV-infected patients has raised ethical problems, which have not yet been completely re-solved. However, currently most groups agree that HIV-infected patients should receive the same treatment as other patients and be included on waiting lists under the same conditions[54].

The pretransplant evaluation of donors and recipients should be the same as for non HIV-infected patients. With respect to the type of donor to be used in HIV-infected patients, most solid organ transplants were carried out using cadaveric donors. In recent years, and as a consequence of the increased demand for organs, the number of living donors has increased. Nevertheless, the benefits of this technique have yet to be demonstrated in the HIV-infected population.

Issues to consider in the posttransplant period

After OLT, patients and physicians start a new and complex clinical situation. Patients must receive a large quantity of medication and this can compromise adherence. In addition to cART, which they may be accustomed to, they must take immunosuppressive drugs and the habitual prophylaxis against opportunistic infections and other medications to manage complications that frequently develop after OLT (e.g. diabetes, hypertension). Patients on methadone programs must continue with this. The HCV-coinfected patients may require therapy with interferon and ribavirin. In this new scenario several issues must be considered such as, the course of HIV infection, immune suppression and allograft rejection, pharmacological interactions among the different type of drugs used and the course of HCV and HBV infection recurrence.

Patients usually follow the same cART regimens that they took during the pre-OLT period, but these regimens can be changed in the post-OLT period on an individual basis in order to choose the easiest regimen to adhere to, with lower potential for pharmacologic interactions with immunosuppressive agents and anti-HCV drugs, and lower liver toxicity. In any case, we should follow the general recommendations for antiretroviral therapy in adults[49,50], and liver function must be closely monitored in order to

detect hepatotoxicity. Furthermore, HIV-infected patients require adequate support during all the post-transplant timeline and they must understand the importance of a correct adherence to all their treatment schedules.

There are solid data showing that HIV-infected patients do not have an increased risk of postoperative complications or a higher incidence of opportunistic infections or tumors than HIV-negative patients[6,55,56]. The CD4 cell counts and plasma HIV viral loads remain stable and undetectable, respectively, as long as cART can be administered. Furthermore, immunosuppressive drugs (e.g. calcineurin inhibitors, mycophenolic acid, prednisone) can reduce HIV replication in two ways: first, by reducing the immune activation induced by HIV; and, second, because calcineurin inhibitors and mycophenolic acid have direct anti-HIV activity[14,21]. Furthermore, mycophenolic acid enhances abacavir action against HIV[57].

Immunosuppression and rejection issues

There are no specific immunosuppressive regimens for HIV-infected patients, and each centre uses the same regimens as for HIV-negative patients. As mentioned previously, the use of standard immunosuppressive therapy in patients with well-controlled HIV-infection did not increase their susceptibility to opportunistic infections or malignant conditions[6,55,56]. Therefore, HIV-infected patients should follow the same prophylaxis protocols as the general population. In some studies, the rates of allograft rejection were higher than in the HIV-negative population. The cause of this phenomenon is unknown, and it is particularly noticeable in kidney transplants, suggesting that HIV does not protect against allograft rejection[33,58,59]. At present, the best regimen of immune suppression in OLT HIV-infected recipients is unknown.

Pharmacologic interactions

There are important pharmacologic interactions between antiretrovirals and immu-nosuppressive or anti-HCV drugs which may be clinically relevant[52,53] that are summarized in table 3.

Cyclosporine A, tacrolimus, and sirolimus are metabolized in the liver using cytochrome P-450, whereas mycophenolate mofetil undergoes glucuronization in the liver. Antiretrovirals can act as inhibitors or inducers of these enzymatic systems. When they act as enzyme inhibitors (e.g. protease inhibitors [PI]), they increase concentrations of these immunosuppressants and can lead to toxicity. For this reason, doses must be markedly reduced (e.g. tacrolimus 1 mg/week in patients taking Kaletra®)[60-62]. These interactions have caused some episodes of acute rejection in patients who stopped PI while taking calcineurin inhibitors. On the other hand, when antiretrovirals act as enzyme inducers (e.g. non-nucleoside reverse transcriptase inhibitors [NNRTI]), they reduce drug levels and can trigger rejection, and therefore doses of most immunosuppressive drugs must be increased[63]. Therefore, it is important to know very well the possible drug interactions and closely monitor the levels of immunosuppressive drugs. In addition, there are important overlapping acute and chronic toxicities between antiretroviral and immunosuppressive drugs that should be taken into account (e.g. liver, renal and/or bone marrow toxicities, hyperlipidemia, diabetes, osteoporosis)[49-50]. As a consequence of these important interactions between some antiretroviral families (i.e. NNRTI or PI) and immunosuppressive drugs, some researchers are using enfuvirtide plus two nucleoside reverse transcriptase inhibitors (NRTI) in order to avoid these interactions[64]. It is important to highlight that the introduction of new families of antiretrovirals with safer profiles of interactions could be very useful in the future. Raltegravir, an HIV-1 integrase inhibitor, could be an example of this because it does not share routes of metabolization with any of the commonly used immunosuppressors drugs, and therefore it would not be necessary to modify its dosification. Although sporadic cases of the use of this drug in this setting have been published[65], more infor-

Table 3. Drug interactions between antiretroviral agents and immunosuppressive drugs

Drug	Mycophenolate mofetil	Cyclosporin A	Sirolimus	Tacrolimus
Abacavir	Both abacavir and MMF are eliminated mainly by glucuronidation. However, clinically important drug-drug interactions have not been reported.			
Amprenavir	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of immunosuppressive drugs may be required. TDM of CsA, SRL and TAC is recommended.*		
Didanosine	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.			
Efavirenz	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Minimal interactions with EFV and CsA or TAC are expected. Some patients needed an initial CsA dose of 350-450 mg b.i.d. followed by a maintenance dose of 250-400 mg b.i.d. TDM of CsA, SRL and TAC is recommended.		
Indinavir	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of CsA and TAC may be required. Some patients needed an initial CsA dose of 75-100 mg b.i.d., followed by a maintenance dose of 75 mg b.i.d. TDM of CsA, SRL and TAC is recommended.*		
Lamivudine	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely. However, as lamivudine is primarily renally excreted, nephrotoxic drugs could impair its elimination.			
Lopinavir/ ritonavir	Theoretically, MMF glucuronidation could be increased (and blood levels reduced) by RTV.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of CsA may be required. Some patients needed an initial dose of 25 mg b.i.d of CsA. Patients on LPV/r + TAC may need a dose reduction to 1 mg once weekly or even less. When LPV/r is initiated in a patient on TAC, the next TAC dose may need to be delayed for between 3-5 weeks, depending on hepatic function. TDM of CsA, SRL and TAC is recommended.*		
Nelfinavir	Theoretically, MMF glucuronidation could be increased (and blood levels reduced) by NFV.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of CsA, TAC and SRL[†] may be required. Some patients needed an initial dose of 50-75 mg b.i.d of CsA, followed by a maintenance dose of 25 mg b.i.d. Some patients on TAC + NFV required a 40 to 70 fold dose-reduction (to 0.5 mg q.d. or even less). TDM of CsA, SRL and TAC is recommended.*		
Nevirapine	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Theoretically, may require increased immunosuppressive drug dosage. Minimal interactions with CsA and NNRTI are expected. Some patients needed an initial dose of 200-250 mg b.i.d of CsA, followed by a maintenance dose of 100-175 mg b.i.d. TDM of CsA, SRL and TAC is recommended.		
Ritonavir	Theoretically, MMF glucuronidation could be increased (and blood levels reduced) by RTV.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of cyclosporine may be required. TDM of CsA, SRL and TAC is recommended.*		
Saquinavir	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Risk of increased drug levels/toxicity of immunosuppressive drugs. Markedly lower doses of CsA may be required. TDM of CsA, SRL and TAC is recommended.*		
Stavudine	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.			
Tenofovir	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Increased risk of nephrotoxicity	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.	Increased risk of nephrotoxicity
Zalcitabine	Theoretically, based on the elimination pathways, a pharmacokinetic drug-drug interaction is unlikely.			
Zidovudine	Both zidovudine and MMF are eliminated mainly by glucuronidation. However, clinically important drug-drug interactions have not been reported.			

b.i.d: twice daily; CsA: cyclosporin A; EFV: efavirenz; LPV/r: lopinavir/ritonavir; MMF: mycophenolate mofetil; NFV: nelfinavir; q.d.: once daily; SRL: sirolimus; TAC: tacrolimus; RTV: ritonavir; TDM: therapeutic drug monitoring; NNRTI nonnucleoside reverse transcriptase inhibitor.

*The antiretroviral is an inhibitor of the P450 isoform CYP3A, which is the primary elimination pathway of CsA, SRL y TAC. Co-administration with the antiretroviral may result in increased plasma concentrations of these immunosuppressive drugs. Patients on protease inhibitors require markedly lower doses of cyclosporine, with continued lowering of the cyclosporine dose over time and ongoing cyclosporine trough monitoring because of progressively increasing cyclosporine bioavailability.

[†]Even with one fifth of the recommended dose of NFV (250 mg/12h), a ninefold increase in sirolimus trough concentration, threefold increase in peak concentration, and 60% increase in the area under the concentration curve 0 to 24 hours has been observed in a liver transplantation patient, compared with patients who were not on NFV.

mation is needed in order to guarantee a broader use of this antiretroviral drug in this scenario.

On the other hand, there also are important pharmacodynamic interactions between some NRTI (e.g. didanosine, stavudine and zalcitabine) and ribavirin, a drug used in combination with pegylated interferon to treat HCV infection recurrence in OLT recipients. These interactions have been reviewed in-depth elsewhere[66].

Finally, given the speed with which new antiretrovirals appear and thus generate unknown interactions, physicians are recommended to consult updated databases on drug interactions[52,53].

Course of HCV infection recurrence

After OLT, HCV infection recurrence is universal, regardless of whether the patient is infected by HIV or not. Some studies have suggested that HCV recurrence in coinfected patients tends to be more severe and occurs earlier[17,67]. Similarly, there is insufficient experience on the efficacy and safety of therapy with interferon and ribavirin in HIV/HCV-coinfected transplant patients. One study[6] summarized the reports evaluating the effectiveness of HCV reinfection treatment in OLT with pegylated interferon plus ribavirin. These patients were treated when they had histological criteria. Only 12 (18.5%) out of 65 HCV/HIV-coinfected patients achieved a sustained virologic response[14,16,17,68-70] (Table 4).

New strategies are necessary to improve the outcome of HCV recurrence in this setting. In this regard, a recent German study showed that sustained virologic response was obtained in six out of seven patients treated within the first three months after OLT[71].

A rapid progression of HCV-related liver disease in HIV-infected recipients would represent a major drawback and would lead to a shortened life expectancy of these patients. In fact, currently it is the most important cause of death. A French study observed that the progression to fibrosis ($\geq$ F2) was significantly higher in the group of HIV infected patients (p < 0.0001)[23.]

Another U.S. study[17] demonstrated a higher rate of cirrhosis at five years in the HIV/HCV-coinfected population who underwent OLT compared to the HCV-monoinfected population (59 vs. 24%; p = 0.03). These two single-centre studies observed that the survival rate at five years is lower in coinfected patients, as has been reported previously.

Finally, a recent study has described two cases of spontaneous clearance of RNA HCV after OLT. This phenomenon is very infrequent and its pathogenic mechanism is not known[72].

Course of HBV infection

Replication of HBV is a contraindication for OLT, so only patients without plasma DNA HBV viremia are accepted for OLT. As HBV infection recurrence can be successfully prevented using hepatitis B immunoglobulins and anti-HBV drugs (lamivudine, tenofovir, adefovir), the outcome of HBV infection after OLT is much better. Adefovir and tenofovir have proven useful against HBV and could be used in cases of resistance to lamivudine. The HIV-positive patients who require antiretroviral therapy and have a chronic HBV infection can use lamivudine (or emtricitabine) and tenofovir as part of triple antiretroviral therapy[73].

Probably due to the low incidence of HBV reinfection, the short- and medium-term survival rate in HBV/HIV-coinfected patients is high and similar to that observed in HBV-monoinfected patients[19,74].

Course of hepatocellular carcinoma

It is well known that hepatocellular carcinoma (HCC) has a faster and worse outcome in HIV/HCV-coinfected people compared with HCV-monoinfected patients[75,76].

Survival of HCV/HBV-monoinfected patients with HCC detected by screening has improved in recent years due to the greater chance of curative

Table 4. Summary of the studies evaluating the effectiveness of the treatment of HCV reinfection in orthotopic liver transplantation with pegylated interferon plus ribavirin

Author, year of publication	HIV/HCV-coinfected patients		Non-HIV HCV-monoinfected patients (control group)	
	No. of cases	SVR[a] No. (%)	No. of cases	SVR[a] No. (%)
Fung, et al. 2004[14]	12	2 (17%)	–	–
Duclos-Vallee, et al. 2006[16]	13	2 (15%)	–	–
de Vera, et al. 2006[17] *	15	4 (27%)	27	7 (28%)[†]
Vennarecci, et al. 2006[68] ‡	9	0 (0%)	–	–
Castells, et al. 2007[69] #	5	1 (20%)	9	1 (11%)
Spanish study, 2007[70]	16	4 (25%)	–	–
Total	65	12 (18.5%)	–	–

SVR: sustained virologic response.
*Most cases were genotype 1; three patients were treated with classical interferon plus ribavirin.
†Rate of sustained virologic response was not specified; data show the rate of virologic response (clearance of HCV RNA from serum).
‡The authors did not specify the type of interferon used.
#These patients were included in the Spanish study and were not taken into account for the overall response rate.
Miro, et al.[6]

treatment with the advent of liver transplantation and radiofrequency ablation[77].

Preliminary Italian experience showed good results in seven HIV-1-infected patients with HCC who underwent OLT. They observed an 86% overall patient and graft survival rate after a mean follow-up period of eight months. They recommend OLT in HIV-infected patients with early stage HCC[78,79].

Conclusions

All HIV-infected patients with ESLD should be considered as candidates for OLT if they meet the HIV inclusion criteria stated here. There is increasing experience with OLT in HIV-infected patients and current data show that short- and mid-term survival is the same as that of HIV-negative patients. The HIV infection can be easily controlled with antiretroviral therapy during the posttransplant period. The evaluation and the pre- and post-OLT management of this complex scenario should include an interdisciplinary team composed of members of the OLT team (hepatologists and surgeons), infectious diseases and HIV specialists, psychologists, social workers and members of alcohol and other drug detoxification programs. Interactions between immunosuppressive agents and antiretrovirals, especially PI and, to a lesser extent, NNRTI, are important and require close monitoring of immunosuppressor plasma levels. Patients do not have a greater risk of opportunistic infections or tumors, and therefore should follow the same prophylaxis protocols as the non HIV-infected population. In patients receiving OLT for HCV cirrhosis, recurrence of the HCV infection is universal during the posttransplant period and it is the main concern. It is unknown whether this reinfection has a worse outcome than in HIV-negative patients and there is insufficient experience with pegylated interferon and ribavirin in this population. However, preliminary data showed low rates of cure (around 20%). The outcome of patients who have received a transplant due to HBV cirrhosis seems to be much better since there is an efficacious prophylaxis against recurrence (HBV-specific immunoglobulin and anti-HBV drugs).

Future research needs

There are several issues that should be explored in the future:

1. Since survival is much shorter in HIV-coinfected patients, strategies to make OLT available sooner after patient assignment to this procedure should be underlined.

2. Currently, there are many sites with active OLT programs in HIV-infected patients, but the number of cases is too small in each single institution to obtain valuable clinical information. The NIH-sponsored multicentre OLT trial (2005-07) that is being performed in the USA will be very useful. A FIPSE-founded study (2006-08) is also being performed in Spain. For these reasons, it would be important to create an International Registry of cases, using standardized CRF in order to know the mid-term (5 year) and long-term (10 year) survival of OLT in HIV-infected patients and to compare it with the non HIV-infected population.

3. To improve the management of pharmacokinetic and pharmacodynamic interactions between immunosuppressive, antiretroviral and anti-HCV drugs.

4. To know the most adequate immunosuppressive regimens for HIV-infected recipients.

5. To know the natural history of OLT HCV reinfection and to improve the management and the treatment of HCV recurrence.

Prospective studies evaluating the effectiveness of pretransplant anti-HCV therapy in HIV-infected patients or the early (preemptive) post-OLT anti-HCV therapy are warranted.

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