Surg Today (2011) 41:1325–1331
DOI 10.1007/s00595-010-4556-x

SURGERY TODAY

Review Article

Liver Transplantation for Patients with Human Immunodeficiency Virus and Hepatitis C Virus Coinfection with Special Reference to Hemophiliac Recipients in Japan

Susumu Eguchi[1], Akihiko Soyama[1,2], Masaaki Hidaka[1], Mitsuhisa Takatsuki[1], Izumi Muraoka[1], Tetsuo Tomonaga[1], and Takashi Kanematsu[1]

[1] Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
[2] Japan Foundation for AIDS Prevention, Tokyo, Japan

Abstract
Liver transplantation for patients with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) remains challenging. The advent of highly active antiretroviral therapy (HAART) for HIV has reduced mortality from opportunistic infection related to acquired immunodeficiency syndrome dramatically, while about 50% of patients die of end-stage liver cirrhosis resulting from HCV. In Japan, liver cirrhosis frequently develops after HCV–HIV coinfection resulting from previously transfused infected blood products for hemophilia. The problems of liver transplantation for those patients arise from the need to control calcineurin inhibitor with HAART drugs, the difficulty of using interferon after liver transplantation with HAART, and the need to control intraoperative coagulopathy associated with hemophilia. We review published reports of liver transplantation for these patients in the updated world literature.

Key words Liver transplantation · Hepatitis C virus · Human immunodeficiency virus · Coinfection · Highly active antiretroviral therapy

Introduction

According to a report compiled by the Japanese Ministry of Health, Labour and Welfare in October 2006, the number of HIV-infected patients in Japan was 8071 (6275 males and 1796 females), and this number has increased further since.[1] In 2008 there were 1557 new cases reported, including 1126 HIV-positive cases and 431 acquired immunodeficiency syndrome (AIDS) cases.[2] The possible routes of infection include sexual contact, through contaminated or unheated blood products, and mother-to-child transmission. When HIV infection is contracted through blood products, there is often coinfection with HCV.

Since 1995, there has been a major change in the cause of death of HIV-infected patients. It is believed that the major factor contributing to these trends is the improved HIV control achieved in recent years with highly active antiretroviral therapy (HAART).[3] HAART is defined as a combination of drugs from different classes of HIV therapy, comprising nucleoside reverse transcriptase inhibitors (NRTIs), and either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or a protease inhibitor (PI). If the compliance is 95% or more, this therapy is successful in more than 50% of patients.[3–5]

This review focuses on liver transplantation in Japanese patients with HIV and HCV, especially those in whom the disease was caused by receiving contaminated blood products in the past and who may be candidates for liver transplantation.

Epidemiology of HIV–HCV Coinfection in Patients with Hemophilia in Japan

According to a survey by the Ministry of Health, Labour and Welfare in the 2008 fiscal year in Japan, 602 patients with hemophilia A (factor 8 deficiency) and 183 with hemophilia B (factor 9 deficiency) were alive with HIV infection (Table 1).[6] Among these, 524 with hemophilia A (87%) and 162 with hemophilia B (89%) also had HCV infections and liver disease (Table 2). Of the 524 persons with hemophilia A, 33 (6.3%) had cirrhosis, 5 (0.9%) had liver cancer, and 2 (0.4%) had liver failure. Two of these patients underwent a liver transplant procedure. It is highly possible that about 50 of the patients

Reprint requests to: S. Eguchi
Received: May 8, 2010 / Accepted: November 9, 2010
This article is a secondary publication, based on a review first reported in the *Japanese Journal of Transplantation* 2010;45(1): 46–53 with full references.

Table 1. Coagulation disorders in Japan

	Hemophilia				
	A	B	VWD	VWD-related disease	Total
Total	4211	916	892	452	6471
Male	4185	908	406	246	5745
Female	29	8	486	206	726
HIV negative					
Total	3609	733	885	448	5675
Male	3583	725	404	245	4957
Female	26	8	481	203	718
HIV positive					
Total	602	183	7	4	796
Male	602	183	2	1	788
Female	0	0	5	3	8

Source: Official Report of the National Surveillance on Coagulation Disorders in Japan, 2008
HIV, human immunodeficiency virus; VWD, von Willebrand disease

Table 2. Stage of liver disease in patients with hemophilia and HIV infection (only reported surviving cases with HCV coinfection)

	No hepatitis	Acute hepatitis	Chronic hepatitis	Liver cirrhosis	HCC	Liver failure	Cured with IFN	Spontaneous cure	LT	Total
Hemophilia A	45	2	350	33	5	2	59	26	2	524
Hemophilia B	15	1	100	11	6	0	19	8	2	162
Total	60	3	450	44	11	2	78	34	4	686

Source: Official Report of the National Surveillance on Coagulation Disorders in Japan, 2008
HIV, human immunodeficiency virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LT, liver transplantation; IFN, interferon

with cirrhosis may be candidates for liver transplantation in the future. In fact, this survey revealed that one-third of the deaths of HIV–HCV coinfected patients with blood-borne diseases were caused by liver disease.

A characteristic that should be taken into account when using imported blood products is that the proportion of patients with HCV genotype 1b is low, at 25% vs 70% in general for Japanese, and the proportion of patients with HCV genotype 3a is high, at 23%. Also, one study found that the proportion of patients with HIV–HCV coinfection with an HCV titer below the level of sensitivity of the assay was significantly lower than the proportion of such patients among non-HIV cases of HCV infection, at 44.0% vs 55.4%, respectively.[7] There have been a few reports from other countries on the problems associated with HCV and HIV infections in hemophiliac patients.[8,9]

Liver Transplantations in HIV–HCV Coinfected Patients

Indications for Liver Transplantation in Patients with HIV–HCV Coinfection

Regardless of the presence of hemophilia, the indications for and methods of liver transplantation are the same for patients with HIV–HCV coinfection. Therefore, information on liver transplantation for HIV–HCV coinfected patients without hemophilia is presented in this section. In fact, after successful liver transplantation, hemophilia can normally be cured. In principle, as for a non-HIV-infected patient, liver transplantation is indicated for patients with type C cirrhosis in liver failure and no expectation of a long-term prognosis.[10–14] Liver transplantation is also indicated for patients not yet in liver failure, but with severe liver damage caused by HAART, especially those with chronic hepatitis C, who need to suspend or stop HAART.[15–18] For patients receiving HAART, the indication needs to be considered in terms of both hepatic reserve and status of the HIV infection. Liver transplantation may also be indicated for hepatocellular carcinoma that develops during follow-up.[19] The conditions for liver transplantation are often defined as follows: AIDS symptoms have not surfaced; the CD4+ lymphocyte count is 200–250/μl or above; and as a result of HAART, the amount of HIV in the blood is below the level of sensitivity of the assay. However, there are cases of pancytopenia resulting from portal hypertension and, as such, some institutions believe that the criterion for liver transplantation resolved be a CD4+ lymphocyte count of 100/μl or more.[19–22] Therefore, an issue to be resolved is whether

the indication can be based solely on a CD4+ lymphocyte count. Although a ratio of CD4 to CD8 lymphocyte count of 14% or greater is also considered an indication, individual institutions still refer to their own criteria. A recent study found a significant correlation between the preoperative model for end-stage liver disease (MELD) score and the postoperative survival rates of HIV–HCV coinfected patients: this also warrants investigation.[23]

Results of Liver Transplantation for Patients with HIV–HCV Coinfection

Liver transplantation from deceased donors has been performed in HIV patients since the 1980s in the United States and Europe. Initially the results were poor, with survival rates of only about 47%,[24] but this has improved remarkably since the introduction of HAART (Table 3). According to a review article published in 2004, 51 HIV-positive patients received liver transplantation between 1996 and 2004 worldwide, with liver damage caused by HCV being the indication in 68%. Since 1997, liver transplantation has been performed in 29 HIV patients at the University of Pittsburgh: 26% of these patients were hemophiliac and 89% were HCV-positive.[25] According to a retrospective study by the United Network for Organ Sharing, involving 138 HIV-positive persons and 30520 HIV-negative persons and evaluating liver transplantation, from 1997 when HAART was introduced and thereafter, the prognosis of patients who were only HIV-positive was relatively good.[26] In this study, the prognosis of HIV–HCV coinfected patients was worse than that of patients who were positive only for HIV. A series of reports are listed in Table 3.[13,20,21,25–34] In reality, in addition to those listed there have been many sporadic reports, such as reviews, regarding expectations for liver transplantation, and assessments of indications.

A recent important study in France, on 14 patients, provided details on interferons, HAART therapy, and liver fibrosis.[33] In all patients, the preoperative amount of HIV in the blood was below the level of sensitivity, and the CD4+ T-cell counts ranged from 85 to 1015. As for calcineurin inhibitors, tacrolimus 0.5 mg per week was started in the 2nd week after surgery in principle; however, there were five cases (36%) of an overdose. HAART was recommenced in the 2nd week after surgery, resulting in the long-term administration of steroids. Liver biopsies in the 12th month after liver transplantation revealed one case of fibrosing cholestatic hepatitis (FCH), one case of fibrosis stage F3, two cases of F2, and five cases of F1. The prognosis after transplantation was thought to be encouraging, since there was only one death as a result of FCH in the series.

Living Donor Liver Transplantation for Patients with HIV–HCV Coinfection

The Koike Group of the Ministry of Health, Labour, and Welfare reported seven cases of living donor liver transplantation (LDLT) for HIV–HCV coinfected patients with hemophilia at The University of Tokyo, and one at Hiroshima University.[35,36] The HCV genotypes were 1a and 1b ($n = 1$), 1b and 3a ($n = 1$), 2a ($n = 1$), 2a and 2b ($n = 1$), and 3a and 1b ($n = 1$). The HVC-RNA levels ranged from 2.8 to 1410 kIU/ml, the HIV-RNA levels in two cases were 50 copies/ml or less, being below the sensitivity level, and the CD4+ T-cell counts ranged from 120 to 618/μl and were 250/μl or less in two cases. At the time of the report in 2005, four patients were alive. Small bowel bleeding (suspected cytomegalovirus enteritis) and graft dysfunction were cited as the causes of death of the nonsurviving patients. Interestingly, interferon therapy was given after surgery to the surviving patients, whereas it was suspended in the two patients who died. HAART therapy was not given to one patient on the grounds that the HIV virus disappeared as the interferon treatment progressed. The report stated that the administration of factor 8 products was never required after surgery for patient #1.

Living donor liver transplantation from a hemophilia carrier was reported in 2002,[37] and it seems that LDLT has been performed in up to 10 patients in Japan. As noted in the section on epidemiology, there are some 50 patients coinfected with HIV–HCV from blood products, in whom liver failure has developed. They, like other patients with chronic hepatitis, may be candidates for liver transplantation, so it is necessary to collect sufficient information.

Problems with Liver Transplantation in HIV–HCV Coinfected Patients with Hemophilia

The Blood Concentration of the Calcineurin Inhibitor Used in Combination with HAART Is Increased

The risk of opportunistic infections caused by a delay in starting HAART and the appropriate time to start HAART has not been established. Moreover, early initiation of the therapy is associated with a high risk of drug-induced liver damage.[38,39] A new drug, Ralteglavir, does not interfere with the metabolism of the calcineurin inhibitor, and might reduce the chance of overshooting the trough level of the calcineurin inhibitor.[40]

Progression of HCV Recurrence Is Accelerated in These Patients Compared with Those Who Are Only HIV-Positive[41]

The HIV virus population dynamics manifest via the immune systems, which are targeted by antiviral drugs such as interferon and ribavirin as well as the HAART

Table 3. Reported series of liver transplantation for patients with HIV infection

First author, year, institution (Journal[Ref.])		*n*	Survival	Findings
Ragni, 2003, Pittsburgh	HIV only	24	3-Year 72.8%	Risk factor for mortality after LT
(J Infect Dis[27])	HIV+HCV	15	3-Year 56.9%	CD4+ <200/μl, HAART resume not possible HIV viral load >400 copies/ml
Neff, 2003, Pittsburgh	HIV positive	16	14/16	2 HAART discontinued due to liver damage
(Liver Transpl[28])				13/16 HIV negative before LT CD4+ <200/μl (6/16), <100/μl (2/16) ACR (6/16). FK trough level increased (6/16)
Fung, 2004, Review	HIV positive (total)	51	80%	68% HCV coinfection, 26% hemophilia
(Liver Transpl[25])	(Pittsburgh)	29	20/29	
Norris, 2004, London	HIV+HCV	7	2/7	4 HCV recurrence, died with sepsis
(Liver Transpl[29])	HIV only	7	7/7	HBV no recurrence
Moreno, 2005, Madrid	HIV+HCV	4	3/4	1 died with FCH 17 months after LT
(Liver Transpl[30])				CD4+ <100/μl (2/16) ACR (1/4), no opportunistic infection
Radecke, 2005, Essen	HIV+HCV	5	2/5	2 survived case on HAART
(Liver Int[31])				
Miró, 2007, Barcelona	HIV+HCV	Review	1-Year 50%–55% (without LT)	Indication for LT: CD4+ >100/μl, HIV negative
(J HIV Ther[11])		(n > 200)		SVR rate (post LT) 15%–20%
Schreibman, 2007, Miami	HIV positive	15	3-Year 73.3%	Infectious complication 26.7% vs 8.7% (P = 0.006)
(Transplantation[20])	HIV negative	857	3-Year 79.4%	Indication for LT: CD4+ >100/μl, HIV <200 copies/mm^3
Reiberger, 2008, Vienna	HIV+HCV (post)	31		HCV viral load increased on immunosuppression
(Eur J Clin Invest[32])	HIV+HCV (pre)	20		IFN effective if CD4+ preserved
	HCV only (pre)	25		SVR rate: HIV–HCV (post LT) 28%
	HIV+HCV (post LT) 50%, HCV only (post LT) 56%			
Mindikoglu, 2008, UNOS	HIV positive	138	2-Year 70%, 3-year 66%	All after HAART era, HCV+ poor prognostic factor
(Transplantation[26])	HIV+HCV	58	2-Year 52%	
	HIV negative	520	2-Year 81%, 3-year 77%	
Duclos-Vallée, 2008, France (THEVIC study group)	HIV+HCV	35	2-Year 73%, 5-year 51%	Pre LT MELD score most important factor for mortality
(Hepatology[21])	HCV only	44	2-Year 91%, 5-year 81%	HIV coinfection: fibrosis progression (>F2) quicker LT indication: CD4+ > 100/μl, HIV negative
Samri, 2009, France (multicenter)	HIV+HCV	14	2-Year 93%	LT indication: HIV negative, no AIDS
(J Hepatol[33])				FK and HAART resumed 2 weeks after LT, FK overdose 5/14 (36%) 1 FCH died. 1-year F2 2, F3 1, F4 (FCH) 2
Testillano, 2009, Bilbao	HIV+HCV	12	3-Year 62%	Patient survival, HCV recurrence, FCH not different (P = 0.09) from LT for patients without HIV
(Transplant Proc[34])	HCV only	59	3-Year 84%	

.HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; HAART, highly active antiretroviral therapy; FCH, fibrosing cholestatic hepatitis; LT, liver transplantation; ACR, acute cellular rejection; SVR, sustained virological response; IFN, interferon; UNOS, United Network for Organ Sharing; MELD, model for end-stage liver disease; FK, tacrolimus

drugs.[42–45] The best time to start interferon treatment and other post-transplantation measures to prevent HCV, optimal immunosuppressive regimens, and ways of monitoring drug blood levels are being studied, and further reports are expected.[46–51]

According to a review on the effects of interferon treatment after liver transplantation, the SVR rate ranges from 0% to 50%. This article reported that there had been many side effects in HIV-positive patients, especially caused by anemia and a low white blood cell

count, and that the continuation of treatment for such patients had been made possible by administration of the growth factor.[52]

Some Studies Refer to the Correlation Between T-Cell Counts and Acute Rejection

In practice, some studies showed the rate of acute cellular rejection to be similar, regardless of HIV positivity.[11,53] Induction therapy without steroids has also been attempted,[54] and the rate of opportunistic infection is reported to be similar after organ transplantation in HIV-positive patients.[20] Thus, the number of CD4+ lymphocytes present prior to liver transplantation is an important factor.

HAART Drugs Can Cause Hepatic Toxicity[55]

If HAART drugs induce liver failure, the best HAART drug to use after liver transplantation must be selected carefully. HAART drug toxicity can also induce complications with acute cellular rejection or other hepatic problems after liver transplantation. A liver biopsy may be needed to elucidate the real cause. Noncirrhotic portal hypertension has recently been reported in HIV-positive patients. HAART drugs may be related to those unresolved pathogeneses.[56]

The Control of Infection After Liver Transplantation for HIV–HCV Coinfection Is Based on the Count of CD4+ lymphocytes Obtained During the Perioperative Period

Therefore, the timing of recommencement of the HAART drug and the preoperative CD4+ lymphocytes counts are both important factors. According to previous reports, prophylaxis against bacterial and viral infections seems to be the same as for liver transplantation without HIV infection.[20]

The Presence of Hemophilia Makes It Difficult to Manage the Coagulation Time and Control Bleeding During the Intra- and Postoperative Period Before a Transplanted Liver Starts to Function

Moreover, when considering LDLT and when only carrier-donors exist, an assessment of the risks associated with the resection of the carrier-donor's liver would also be a problem.[37]

Conclusions

This review is an overview of liver transplantation performed to date for HIV–HCV coinfected persons. Although there have been no cadaveric liver transplantations for these patients in Japan,[57] conventional knowledge about cadaveric liver transplantation may be applicable in most cases, despite the unresolved problems. In light of the fact that most of these Japanese patients are the victims of contaminated blood products, we believe that the number of liver transplantations will increase, in the context of medical relief.[58]

Acknowledgment. This work was supported in part by a Grant-in-Aid for Research on HIV/AIDS from the Ministry of Health, Labour and Welfare of Japan.

References

1. Annual report on patients with AIDS. Program entrusted by Ministry of Health, Labour and Welfare, Japan. 2005.
2. Annual report on patients with AIDS. Program entrusted by Ministry of Health, Labour and Welfare, Japan. 2008.
3. Valdez H, Chowdhry TK, Asaad R, Woolley IJ, Davis T, Davidson R, et al. Changing spectrum of mortality due to human immunodeficiency virus: analysis of 260 deaths during 1995–1999. Clin Infect Dis 2001;32:1487–93.
4. del Amo J, Hernández-Aguado I, Pérez-Hoyos S. Effect of antiviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. Lancet 2003;362:1708–13.
5. Pineda JA, Romero-Gómez M, Díaz-García F, Giron-Gonzalez JA, Montero JL, Torre-Cisneros J, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. Hepatology 2005;41:779–89.
6. Japan Foundation for AIDS Prevention. Official report of the national surveillance on coagulation disorders in Japan 2008.
7. Thomas DL. The challenge of hepatitis C in the HIV-infected person. Annu Rev Med 2008;59:473–85.
8. Rumi MG, De Filippi F, Santagostino E, Colombo M. Hepatitis C in haemophilia: lights and shadows. Haemophilia 2004;suppl 4:211–5.
9. Wilde JT. HIV and HCV coinfection in haemophilia. Haemophilia 2004;10:1–8.
10. Kumar R, Singla V, Kacharya S. Impact and management of hepatitis B and hepatitis C virus co-infection in HIV patients. Trop Gastroenterol 2008;29:136–47.
11. Miro JM, Aguero F, Laguno M, Tuset M, Cervera C, Moreno A, et al. Liver transplantation in HIV/hepatitis co-infection. Hospital Clinic OLT in HIV Working Group. J HIV Ther 2007;12:24–35.
12. Castells L, Escartín A, Bilbao I, Len O, Allende H, Vargas V, et al. Liver transplantation in HIV–HCV coinfected patients: a case-control study. Transplantation 2007;83:354–8.
13. Miró JM, Laguno M, Moreno A, Rimola A; Hospital Clinic OLT in HIV Working Group. Management of end stage liver disease (ESLD): what is the current role of orthotopic liver transplantation (OLT)? J Hepatol 2006;44(1 suppl):S140–5.
14. Ragni MV, Eghtesad B, Schlesinger KW, Dvorchik I, Fung JJ. Pretransplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease. Liver Transpl 2005;11:1425–30.
15. Antoniades C, Macdonald C, Knisely A, Taylor C, Norris S. Mitochondrial toxicity associated with HAART following liver transplantation in an HIV-infected recipient. Liver Transpl 2004;10:699–702.
16. Bonacini M. Liver injury during highly active antiretroviral therapy: the effect of hepatitis C coinfection. Clin Infect Dis 2004;38 suppl 2:S104–8.
17. Duclos-Vallée JC, Vittecoq D, Teicher E, Feray C, Roque-Afonso AM, Lombes A, et al. Hepatitis C virus viral recurrence and liver mitochondrial damage after liver transplantation in HIV-HCV co-infected patients. Hepatology 2005;42:341–9.
18. Polard E, Camus C, Abault AY, Turlin B, Arvieux C, Messner M, et al. Retransplantation for acute liver failure due to combined

antiviral agents in an HIV-HCV coinfected liver transplant recipient. Transplantation 2005;80:1136–8.
19. Di Benedetto F, De Ruvo N, Berretta M, Masetti M, Montalti R, DiSandro S, et al. Hepatocellular carcinoma in HIV patients treated by liver transplantation. Eur J Surg Oncol 2008;34: 422–7.
20. Schreibman I, Gaynor JJ, Jayaweera D, Pyrsopoulos N, Weppler D, Tzakis A, et al. Outcomes after orthotopic liver transplantation in 15 HIV-infected patients. Transplantation 2007;84: 697–705.
21. Duclos-Vallée JC, Féray C, Sebagh M, Teicher E, Roque-Afonso A, Roche B, et al. THEVIC Study Group. Survival and recurrence of hepatitis C after liver transplantation in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology 2008;47:407–17.
22. Maida I, Núñez M, González-Lahoz J, Soriano V. Liver transplantation in HIV-HCV coinfected candidates: what is the most appropriate time for evaluation? AIDS Res Hum Retroviruses 2005;21:599–601.
23. Subramanian A, Sulkowski M, Barin B, Stablein D, Curry M, Nissen N, et al. MELD score is an important predictor of pretransplantation mortality in HIV-infected liver transplant candidates. Gastroenterology 2010;138:159–64.
24. Tzakis AG, Cooper MH, Dummer JS, Rangi M, Ward JW, Startzl TE. Transplantation in HIV+ patients. Transplantation 1990; 49:354–8.
25. Fung JJ, Eghtesad B, Patel-Tom K, DeVera M, Chapman H, Ragni M. Liver transplantation in patients with HIV infection. Liver Transpl 2004;10(10 suppl 2):S39–53.
26. Mindikoglu AL, Regev A, Magder LS. Impact of human immunodeficiency virus on survival after liver transplantation: analysis of United Network for Organ Sharing database. Transplantation 2008;85:359–68.
27. Ragni MV, Belle SH, Im KA, Neff G, Roland M, Stock P, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. J Infect Dis 2003;188:1412–20.
28. Neff GW, Bonham A, Tzakis AG, Ragni M, Jayaweera D, Schiff ER, et al. Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. Liver Transpl 2003;9:239–47.
29. Norris S, Taylor C, Muiesan P, Portmann BC, Knisely AS, Bowles M, et al. Outcomes of liver transplantation in HIV-infected individuals: the impact of HCV and HBV infection. Liver Transpl 2004;10:1271–8.
30. Moreno S, Fortún J, Quereda C, Moreno A, Perez-Elias MJ, Martin-Davila P, et al. Liver transplantation in HIV-infected recipients. Liver Transpl 2005;11:76–81.
31. Radecke K, Frühauf NR, Miller M, Ross B, Köditz R, Malagó M, et al. Outcome after orthotopic liver transplantation in five HIV-infected patients with virus hepatitis-induced cirrhosis. Liver Int 2005;25:101–8.
32. Reiberger T, Rasoul-Rockenschaub S, Rieger A, Ferenci P, Gangl A, Peck-Radosavljevic M. Efficacy of interferon in immunocompromised HCV patients after liver transplantation or with HIV co-infection. Eur J Clin Invest 2008;38:421–9.
33. Samri A, Roque-Afonso AM, Beran O, Tateo M, Teicher E, Feray C, et al. Preservation of immune function and anti-hepatitis C virus (HCV) immune responses after liver transplantation in HIV-HCV coinfected patients (ANRS-HC08 "THEVIC" trial). J Hepatol 2009;51:1000–9.
34. Testillano M, Fernandez JR, Suarez MJ, Gastaca M, Bustamante J, Pijoan JI, et al. Survival and hepatitis C virus recurrence after liver transplantation in HIV- and hepatitis C virus-coinfected patients: experience in a single center. Transpl Proc 2009;41: 1041–3.
35. Treatment guideline for patients with HIV-HCV co-infection. Project (Program) entrusted by Ministry of Health, Labour And Welfare, Japan (Study on hepatic diseases combined to HIV infection). 2005.
36. Sugawara Y, Ohkubo T, Makuuchi M, Kimura S, Tachikawa N. Living-donor liver transplantation in an HIV-positive patient with hemophilia. Transplantation 2002;74:1655–6.
37. Horita K, Matsunami H, Shimizu Y, Shimizu A, Kurimoto M, Suzuki K, et al. Treatment of a patient with hemophilia A and hepatitis C virus-related cirrhosis by living-related liver transplantation from an obligate carrier donor. Transplantation 2002;73: 1909–12.
38. Teicher E, Abbara C, Duclos-Vallee JC, Antonini T, Bonhomme-Faivre L, Desbois D, et al. Enfuvirtide: safe and effective antiretroviral agent for human immunodeficiency virus-infected patients shortly after liver transplantation. Liver Transpl 2009;15: 1336–42.
39. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis 2001;33:562–9.
40. Tricot L, Teicher E, Peytavin G, Zucman D, Conti F, Calmus Y, et al. Safety and efficacy of raltegravir in HIV-infected transplant patients cotreated with immunosuppressive drugs. Am J Transplant 2009;9:1946–52.
41. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology 1999;30:1054–8.
42. Lavuer GM,Lucas M, Timm J, Ouchi K, Kim AY, Day CL, et al. Full-breadth analysis of CD8+ T-cell responses in acute hepatitis C virus infection and early therapy. J Virol 2005;79:12979–88.
43. Berenguer J, Alvarez-Pellicer J, Martín PM, Lopez-Aldeguer J, von-Wichmann MA, Quereda C, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology 2009;50: 407–13.
44. Weis N, Lindhardt BO, Kronborg G, Hansen AB, Laursen AL, Christensen PB, et al. Impact of hepatitis C virus coinfection on response to highly active antiretroviral therapy and outcome in HIV-infected individuals: a nationwide cohort study. Clin Infect Dis 2006;42:1481–7.
45. Ciuffreda D, Comte D, Cavassini M, Giostra E, Buhler L, Perruchoud M, et al. Polyfunctional HCV-specific T-cell responses are associated with effective control of HCV replication. Eur J Immunol 2008;38:2665–77.
46. Reiberger T, Rasoul-Rockenschaub S, Rieger A, Ferenci P, Gangl A, Peck-Radosavljevic M. Efficacy of interferon in immunocompromised HCV patients after liver transplantation or with HIV co-infection. Eur J Clin Invest 2008;38:421–9.
47. Castells L, Esteban JI, Bilbao I, Vargas V, Allende H, Ribera E, et al. Early antiviral treatment of hepatitis C virus recurrence after liver transplantation in HIV-infected patients. Antivir Ther 2006;11:1061–70.
48. Moreno A, Bárcena R, García-Garzón S, Muriel A, Quereda C, Moreno L, et al. HCV clearance and treatment outcome in genotype 1 HCV-monoinfected, HIV-coinfected and liver transplanted patients on peg-IFN-alpha-2b/ribavirin. Hepatology 2005;43: 783–90.
49. Gruber SA, Doshi MD, Cincotta E, Brown KL, Singh A, Morawski K, et al. Preliminary experience with renal transplantation in HIV+ recipients: low acute rejection and infection rates. Transplantation 2008;86:269–74.
50. Rafecas A, Rufí G, Figueras J, Fabregat J, Xiol X, Ramos E, et al. Liver transplantation without steroid induction in HIV-infected patients. Liver Transpl 2004;10:1320–3.
51. Guaraldi G, Cocchi S, Codeluppi M, Di Benedetto F, Bonora S, Pecorari M, et al. Role of therapeutic drug monitoring in a patient with human immunodeficiency virus infection and end-stage liver disease undergoing orthotopic liver transplantation. Transplant Proc 2005;37:2609–10.

52. Fredrick RT, Hassanein TI. Role of growth factors in the treatment of patients with HIV/HCV coinfection and patients with recurrent hepatitis C following liver transplantation. J Clin Gastroenterol 2005;39(1 suppl):S14–22.
53. Gruber SA, Doshi MD, Cincotta E, Brown KL, Singh A, Morawski K, et al. Preliminary experience with renal transplantation in HIV+ recipients: low acute rejection and infection rates. Transplantation 2008;86:269–74.
54. Tan HP, Kaczorowski DJ, Basu A, Khan A, McCauley J, Marcos A, et al. Living-related donor renal transplantation in HIV+ recipients using alemtuzumab preconditioning and steroid-free tacrolimus monotherapy: a single center preliminary experience. Transplantation 2004;78:1683–8.
55. Turkova A, Ball C, Gilmour-White S, Rela M, Mieli-Vergani G. A paediatric case of acute liver failure associated with efavirenz-based highly active antiretroviral therapy and effective use of raltegravir in combination antiretroviral treatment after liver transplantation. J Antimicrob Chemother 2009;63:623–5.
56. Mendizabal M, Craviotto S, Chen T, Silva MO, Reddy KR. Noncirrhotic portal hypertension: another cause of liver disease in HIV patients. Ann Hepatol 2009;8:390–5.
57. Yoshimura N, Okajima H, Ushigome H, Sakamoto S, Fujiki M, Okamoto M. Current status of organ transplantation in Japan and worldwide. Surg Today 2010;40:514–25.
58. Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. Lancet 2011;377:1198–209.