Clinical Study

Long-Term Outcome of Liver Transplantation in HIV-1-Positive Patients: 15-Year Follow-Up

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Liver transplantation (LT) for patients with human immunodeficiency virus type-1 (HIV-1) infection has been associated with poor outcome. However, after the introduction of the highly active antiretroviral therapy, short-term patient survival after LT has improved significantly. We examined the long-term outcome of HIV-1-positive patients who underwent LT. Medical records were analysed in nine HIV-1-positive LT patients who underwent LT from August 1998 to May 2012. Eight were known to be HIV-1 positive at the time of listing for LT and had end-stage liver disease (ESLD) due to hepatitis C. One patient had primary biliary cirrhosis, and primary HIV-1 infection was found at the date of LT. Seven of the nine patients remain alive to date. So far, three have survived more than 12 years after LT. The overall patient survival rate for both five and 10 years is 77.8%. Four patients experienced acute rejection and six acquired biopsy-confirmed HCV recurrence. HIV-1 replication was effectively blocked during follow-up in all patients. We conclude that long-term survival of HIV-1-positive patients after LT can be achieved. Our study suggests that LT can offer an effective treatment option in selected HIV-1 infected patients with ESLD.

1. Introduction

Orthotopic liver transplantation (LT) is an established treatment modality for patients with end-stage liver disease (ESLD), liver malignancy with certain conditions, and some metabolic liver disorders. The short- and long-term graft and patient survival have been improved with the refinement of transplant indications, modification of surgical techniques, and postoperative management with new immunosuppressive protocols [1]. It has been possible to expand indications for LT due to more advanced management of coexisting diseases. LT for ESLD in patients with human immunodeficiency virus type 1 (HIV-1) infection has been controversial and has previously been regarded as an absolute contraindication in some transplantation centres. This was due to early reports indicating poor outcome after LT in HIV-1 infected patients at the time of LT or acquired HIV at or soon after LT [2]. Other institutes also reported poor short-term survival rate before the introduction of highly active antiretroviral therapy (HAART) [3, 4]. However, the improved management of HIV-1 infections with HAART, introduced in the mid-1990s, significantly decreased HIV related morbidity and mortality in infected patients [5, 6]. Many HIV-1 infected patients are coinfected with hepatitis C virus (HCV) and/or hepatitis B virus (HBV). Hence, liver disease has become a significant cause of mortality in HIV-infected patients. Patients coinfected with HIV-1 and HCV have higher HCV RNA levels, and have more rapid progression of hepatic fibrosis to ESLD than HCV monoinfected patients [7]. The management of ESLD should be prioritised in order to improve the life expectancy for these patients. Therefore, LT for HIV-infected patients has gained
new attention. We started our liver transplantation program for HIV-1-positive patients in 1998 and have previously reported initial short-term outcome and clinical management of these patients after LT [8–10]. Lately, several reports have indicated improved short-term outcome after LT for HIV-1 infected patients after the introduction of HAART [11–18]. Limited data, however, exists on the long-term outcome in HIV-1/HCV coinfected patients after LT, in particular follow-up of more than 10 years [18]. Additional data that describe the long-term outcome from single centres, with detailed and precise clinical information, is needed besides studies based on analyses of databases [13, 19].

In the present study, we retrospectively analysed nine HIV-positive patients who underwent LT due to ESLD caused by HCV/HBV. We evaluated clinical parameters including management of HIV and HCV/HBV infection and analysed long-term outcome in these patients.

2. Materials and Methods

2.1. Patients. This study is a retrospective cohort analysis of 10 LT in nine HIV-1 infected patients (eight male and one female) which were performed at the Department of Transplantation Surgery, Karolinska University Hospital in Stockholm, Sweden, from August 1998 to May 2012. Organ donors’ information, intraoperative parameters, patients pre- and postoperative parameters, including CD4⁺ cells, CD8⁺ cells, HIV RNA, HCV RNA, and HBV DNA, and results of liver biopsy in these recipients were acquired from the patients’ medical records. Placement of the patients on the waiting list for LT was decided at a multidisciplinary conference with transplant surgeons, anesthesiologists, hepatologists, radiologists, and infectious disease specialists. Our principal criteria for LT in HIV-1-positive patients were standard criteria for non-HIV-1 infected ESLD patients, in addition, a CD4⁺ cell count >100 cells/µL, undetectable serum HIV-viral levels (<50 copies/µL), no previous acquired immune deficiency syndrome (AIDS) episode (except episodes of tuberculosis, pneumocystis pneumonia, and candida infection), and no alcohol use for at least the past six months. Characteristics of patient/donor and operation factors are given in Tables 1 and 2. One patient (patient number 5) underwent retransplantation six months after the initial LT due to a graft failure with cholestasis. The follow-up period ranged between 1.3 and 15.0 years.

2.2. Preoperative and Early Postoperative Management for HIV Infection. Eight of the HIV-1-positive patients were coinfected with HCV before LT. One patient also had HBV coinfection (patient number 9). Patient number 3 underwent LT due to primary biliary cirrhosis (PBC) and was negative for anti-HIV-1 antibodies when accepted to the waiting list. He was diagnosed with primary HIV-1 infection (PHI) on the day of LT by both clinical symptoms (headache, tiredness, and fever seven days before LT and these symptoms continued for three days), and laboratory analysis (positive HIV p24 antigen and HIV-1 RNA, negative HIV-1 antibodies, and isolation of HIV-1 were from plasma and blood cells on the day of LT) [8]. All patients except patient number 2 had undetectable HIV-1 RNA levels before LT. Patient number 5 had less than 100 cell counts/µL before LT and re-LT. The other seven patients with chronic HIV-1 infection had greater than 100 cell counts/µL before LT.

As HAART regimen, we used multiple antiviral drugs as follows: lamivudine (3TC), stavudine (d4T), nelfinavir (NFV), nevirapine (NVP), lopinavir/ritonavir (LPV/r), abacavir (ABC), didanosine (ddI), zidovudine (ZDV), raltegravir (RAL), tenofovir (TDF), emtricitabine (FTC), enfuvirtide (ENF), atazanavir (ATV), and efavirenz (EFV). The pre-LT and latest HAART regimens in these patients are given in Tables 2 and 3. The collection of data was approved by the Swedish Data Inspection Board and the ethical committee at Karolinska Institute, Sweden.

2.3. Pre- and Postoperative Management for HCV and HBV Infection. HCV RNA levels prior to transplantation are shown in Table 2. Patients numbers 6 and 7 had previously received peg-IFN alpha-2a and ribavirin before LT for hepatitis C. After LT, the HCV RNA levels were analysed when the aminotransferase and bilirubin levels increased significantly or following a postoperative routine protocol at three and six months post-LT and, thereafter, yearly. The decision to start anti-HCV therapy was determined by the patients’ liver function and the histological degree of inflammation and fibrosis. Patient number 9 was also HBsAg positive, negative for anti-HBs, positive for anti-HBc, negative for HBeAg, and positive for anti-HBe before LT. He had received 3TC pre- and postoperatively. HBV DNA was undetectable (0 IU/mL) before transplantation. Human specific anti-hepatitis B immunoglobulin (HBIG) was used intra- and postoperatively as a prophylaxis for the reactivation of HBV. HBIG dose was as follows: 5000E i.v. in the anhepatic phase, 2500E i.v. daily during postoperative
Table 2: Characteristics of HIV-infected patients and LT.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age year</th>
<th>Gender</th>
<th>Transmission risk factor</th>
<th>Diagnosis</th>
<th>Pre-LT HAART</th>
<th>Pre-LT CD4+ /µL ref. 490–1340</th>
<th>Pre-LT CD8+ /µL ref. 190–800</th>
<th>Pre-LT HIV RNA copies/mL</th>
<th>Pre-LT HCV RNA (and HBV DNA) IU/mL</th>
<th>LTx date</th>
<th>Liver and operation characteristics</th>
<th>0-liver biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>Transfusion</td>
<td>HIV (PHI) with PBC</td>
<td>ABC, ddI, LPV/r</td>
<td>410</td>
<td>1120</td>
<td>3000</td>
<td>1.3 × 10^6</td>
<td>Jun ’00</td>
<td>Single AA, CCS, CCA, VVB, Double AA, CCS, CCA</td>
<td>Severe steatosis, Severe steatosis, Severe steatosis, Discrete steatosis, Discrete steatosis, Discrete steatosis</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>M</td>
<td>Sexual</td>
<td>HIV (PHI) with PBC</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>&lt;50</td>
<td>(Negative anti-HCV antibody)</td>
<td>Jun ’00</td>
<td>Single AA, CCS, CCA, VVB, Single AA, CCS, CCA</td>
<td>Mild portal fibrosis, Moderate ischemia, Severe ischemia, Severe ischemia, Severe ischemia, Severe ischemia</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>M</td>
<td>Transfusion</td>
<td>Hemophilia A, HIV with HCV</td>
<td>3TC, ZDV, NFV</td>
<td>240</td>
<td>500</td>
<td>&lt;50</td>
<td>2.9 × 10^5</td>
<td>Jan ’01</td>
<td>Triple AA, CCS, CCA, VVB</td>
<td>Mild portal fibrosis, Severe ischemia, Mild ischemia, Severe ischemia, Severe ischemia, Severe ischemia</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>M</td>
<td>Transfusion</td>
<td>Hemophilia A, HIV with HCV</td>
<td>3TC, d4T, ddI</td>
<td>80</td>
<td>NA</td>
<td>&lt;50</td>
<td>NA</td>
<td>May ’01</td>
<td>Triple AA, CCS, CCA, VVB</td>
<td>Mild portal fibrosis, Moderate portal fibrosis, Mild ischemia, No steatosis, No steatosis, No steatosis</td>
</tr>
<tr>
<td>5-1</td>
<td>53</td>
<td>M</td>
<td>Transfusion</td>
<td>Hemophilia A, HIV with HCV</td>
<td>3TC, d4T, ddI</td>
<td>90</td>
<td>360</td>
<td>&lt;50</td>
<td>6.95 × 10^5</td>
<td>Nov ’01</td>
<td>Single AA, CJS, CCA, VVB</td>
<td>Mild focal portal fibrosis, Severe ischemia, Moderate ischemia, Moderate ischemia, Moderate ischemia, Moderate ischemia</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>F</td>
<td>i.v. drugs/sexual</td>
<td>HIV with HCV</td>
<td>3TC, ZDV, RAL</td>
<td>318</td>
<td>532</td>
<td>&lt;20</td>
<td>2.39 × 10^5</td>
<td>Nov ’09</td>
<td>Single AA, CCS, PGB</td>
<td>Mild portal fibrosis, Moderate ischemia, No steatosis, No steatosis, No steatosis, No steatosis</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>M</td>
<td>i.v. drugs/sexual</td>
<td>HIV with HCV</td>
<td>TDF, FTC, LPV/r</td>
<td>238</td>
<td>198</td>
<td>&lt;20</td>
<td>6560</td>
<td>Sep ’10</td>
<td>Single AA, CCS, PGB</td>
<td>Moderate ischemia, No steatosis, No steatosis, No steatosis, No steatosis, No steatosis</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>M</td>
<td>i.v. drugs</td>
<td>HIV with HCV</td>
<td>FTC,TDF, LPV/r</td>
<td>190</td>
<td>110</td>
<td>&lt;20</td>
<td>13900</td>
<td>Aug ’11</td>
<td>Single AA, CCS, PGB</td>
<td>Mild portal fibrosis, Discrete steatosis, No steatosis, No steatosis, No steatosis, No steatosis</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>M</td>
<td>i.v. drugs</td>
<td>HIV with HCV and HBV</td>
<td>3TC, ABC, EFV</td>
<td>230</td>
<td>570</td>
<td>&lt;20</td>
<td>6.39 × 10^5</td>
<td>May ’12</td>
<td>Single AA, CCS, PGB</td>
<td>No portal fibrosis, No portal fibrosis, No portal fibrosis, No portal fibrosis, No portal fibrosis, No portal fibrosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>Outcome</th>
<th>Latest HAART</th>
<th>Latest CD4+/μL</th>
<th>Latest CD8+/μL</th>
<th>Latest HIV-1 PCR copies/mL</th>
<th>Latest HCV RNA (and HVB RNA*) IU/mL</th>
<th>Survival after LT (year)</th>
<th>Postoperative liver biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alive</td>
<td>3TC, ABC, ATV</td>
<td>780</td>
<td>850</td>
<td>&lt;20</td>
<td>0</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence of hepatitis C (6 y 7 m). Mild nonspecific changing with bridging fibrosis, no rejection, and no hepatitis (10 y 1 m).</td>
</tr>
<tr>
<td>2</td>
<td>Deceased Sep'00</td>
<td>3TC, d4T, ddl, LPV/r</td>
<td>410</td>
<td>1170</td>
<td>230</td>
<td>1.01 × 10⁵</td>
<td>0.3</td>
<td>Moderate acute rejection two weeks after LT, RAI = 6 (1 m). Moderate acute rejection with ischemic change (3 m).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild acute rejection (RAI = 3-4) (3 m). Suspect early chronic rejection (RAI = 3) (1 y 3 m). Early chronic rejection, toxic change, RAI = 2 (5y). Slight toxic changing. No fibrosis, no rejection, and no hepatitis (10 y 4 m).</td>
</tr>
<tr>
<td>3</td>
<td>Alive</td>
<td>3TC, ABC, LPV/r</td>
<td>380</td>
<td>350</td>
<td>&lt;20</td>
<td>–</td>
<td>13.2</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ischemic or toxic change (4 m). Recurrence of hepatitis C, fibrosis (1y). Recurrence of hepatitis C. Cirrhotic liver (3 y). Cirrhotic liver, no rejection (5 y).</td>
</tr>
<tr>
<td>4</td>
<td>Alive</td>
<td>3TC, ABC, ZDV</td>
<td>440</td>
<td>610</td>
<td>&lt;20</td>
<td>0</td>
<td>12.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cholestatic liver, bile duct obstruction with cholangitis, no rejection, no hepatitis (4 m). Cholestatic liver, bile duct obstruction with cholangitis, no rejection, and no hepatitis (6 m).</td>
</tr>
<tr>
<td>5-1</td>
<td>Re-LT Nov’01,</td>
<td>3TC, d4T, ddl</td>
<td>90</td>
<td>360</td>
<td>&lt;50</td>
<td>6.85 × 10⁵</td>
<td>1.2</td>
<td>Mild acute rejection without sign of hepatitis (RAI = 3) (1 m). Cholestatic liver with bile duct obstruction or toxic effect and no rejection or hepatitis (2 m). Cholestatic liver without sign of rejection or hepatitis (3 m). Steatosis. Toxic or metabolic effect with acute cholangitis, no rejection, and no hepatitis (2 y). Recurrence of low-grade hepatitis C (3 y).</td>
</tr>
<tr>
<td>5-2</td>
<td>Deceased Jul’02</td>
<td>3TC, d4T, ddl</td>
<td>30</td>
<td>70</td>
<td>&lt;50</td>
<td>1.7 × 10⁶</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Alive</td>
<td>3TC, ABC, RAL</td>
<td>460</td>
<td>580</td>
<td>&lt;20</td>
<td>3.97 × 10⁶</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Alive</td>
<td>TDF, FTC, LPV/r</td>
<td>440</td>
<td>1450</td>
<td>&lt;20</td>
<td>9.92 × 10⁶</td>
<td>3.0</td>
<td>Recurrence of hepatitis C (1 y).</td>
</tr>
<tr>
<td>8</td>
<td>Alive</td>
<td>3TC, LPV/r</td>
<td>390</td>
<td>2280</td>
<td>&lt;20</td>
<td>3.09 × 10⁶</td>
<td>2.0</td>
<td>No rejection and no hepatitis (7 m). Recurrence of hepatitis (1 y). Mild acute rejection (RAI = 4) (0.7 m). Recurrence of hepatitis (1 m). Cholestatic liver, bile duct obstruction and pericholangitis, and recurrence of hepatitis (3 m).</td>
</tr>
<tr>
<td>9</td>
<td>Alive</td>
<td>TDF, FTC, RAL</td>
<td>110</td>
<td>330</td>
<td>&lt;20</td>
<td>1.03 × 10⁷</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

*Only for patient 9. Abbreviations: ATV: atazanavir; RAI: rejection activity index; (m): month; (y): year after transplantation.

days 1–7, then 5000E i.v. every other week from day 8 to the day of discharge, and thereafter 1000E i.m. per week until three months postoperative and later only if the HBsAg titer decreased to <100 IU/mL.

2.4. Graft and Operation Characteristics. All grafts were whole-liver grafts from nine deceased donors and one domino donor from a familial amyloidotic polyneuropathy patient (patient number 2). The first five consecutive LTs were done
with cavocaval anastomosis with venovenous bypass; the following four LTs were done using piggy-back technique. Bile duct reconstruction was choledochocholedochostomy in nine LTs and one choledochojejunostomy for the re-LT case. Eight liver grafts had a single artery and two livers showed multiple arteries and so multiple arterial anastomoses were performed (patients numbers 3 and 5).

2.5. Liver Biopsy. A baseline 0-biopsy was performed after the reperfusion and just before abdominal closure. Postoperative liver biopsies were performed when the aminotransferase and/or bilirubin levels increased significantly or following postoperative control biopsy protocol after six months and one, two, three, five, and 10 years. Diagnosis of acute rejection was based on histopathological examination.

2.6. Immunosuppression after-LT. The first five patients were treated with tacrolimus and steroids, and the remaining four patients were treated with cyclosporine, azathioprine, and steroids as the initial medication. Tacrolimus and cyclosporine medication were adjusted individually by monitoring the trough levels (tacrolimus 5–15 ng/mL, cyclosporine 100–250 ng/mL). Special caution was given to patients who had received protease inhibitors (PIs) due to drug-drug interactions (DDI) over the Cytochrome P 450 3A liver enzyme system causing high blood levels of the immunosuppressive drugs as previously described [9]. One patient was switched from cyclosporine to tacrolimus. Azathioprine was discontinued in three patients: in two due to leukopenia, and one patient was switched to Mycophenolate Mofetil in order to reduce the cyclosporine dose. A steroid cycle, intravenous bolus of methylprednisolone 1000 mg followed by oral tapered prednisone, was used for the patients with acute rejection.

2.7. Statistical Analysis. The median and range were used for the descriptive statistics. The Kaplan-Meier overall graft and patient survival rate were analysed in our patients. The STATISTICA statistical program (StatSoft, Inc., Tulsa, USA.) was used for the analysis. Patient death with functioning graft is counted as graft failure.

3. Results

3.1. Patient Outcome. Table 3 shows the long-term outcome of patients. At the latest follow-up, seven patients were alive and two patients (patients numbers 2 and 5) had died. Patient number 2 died three months after LT due to unknown central nerve system (CNS) failure with a functioning graft. Patient number 5 died 14 months after the initial LT (eight months after retransplantation) due to what was believed to be cholestasis hepatitis with liver failure.

The detailed information of these deceased patients is as follows: patient number 2 was hospitalised for biopsy-confirmed acute rejection, and treatment for the rejection with steroid cycle was started. However, three days after this he was found unconscious due to unknown causes and died the next day. Blood glucose was normal. CT and MRI brain showed no sign of bleeding or infarction and no sign of increased intracranial pressure. Cerebrospinal fluid from this patient was investigated but no evidence of infection including HIV-1 was found and no progressive multifocal leukoencephalopathy, or any other specific cause of death was found. Cultures of urine, blood, and cerebrospinal fluid were all negative. HIV RNA was detected during the entire pre- and postoperative course, 3000 copies/mL when the patient was placed on the waiting list, 15000 copies/mL at LT but decreased to 230 copies/mL 2.5 months after LT. CD4+ counts were greater than 400/µL during the follow-up. HCV RNA was 1.3 × 10⁶ at LT but it decreased to 1.0 × 10⁵ one month after LT without specific HCV treatment. Patient number 5 had a relatively good graft function initially after LT but later displayed bile duct obstruction with cholangitis episodes. He received percutaneous transhepatic cholangiodrainage (PTCD), which did not resolve the problem. Liver biopsies showed cholestatic liver with bile duct proliferation due to bile duct obstruction, cholangitis, and ischemic change without sign of rejection or hepatitis. The patient underwent retransplantation due to cholestatic liver failure six months after the initial LT. After re-LT the patient was treated with intravenous steroids for a biopsy-confirmed acute mild rejection. However, even after retransplantation the patient developed high bilirubin levels and had episodes of cholangitis treated with antibiotics. He did not receive antiviral medication for HIV immediately after the second transplantation and HIV RNA was reactivated to 1200 copies/mL two months after re-LT. The anti-HIV-viral medication regimen with the same protocol as preoperatively (3TC, d4T, ddI) was restarted and HIV copies could not be detected one month later. CD4+ counts were less than 100 counts/µL during the entire pre- and postoperative periods. HCV RNA increased to 1.3 × 10⁶ IU/mL two months after re-LT and treatment with IFN alpha started initially IFN alpha-2b and switched to peg-INF alpha-2a. Scintigraphy showed deteriorated liver function without any bile flow to jejunum. Peg-IFN was discontinued due to no improvement of liver function. The patient received PTCD three months after LT. However, this did not improve bile flow. Biopsy showed cholestatic liver without conclusive signs of hepatitis and no signs of rejection. The patient died eight months after re-LT due to cholestatic liver failure. Again, we did not find any primary surgical/mechanical reason for the cholestasis after re-LT and assumed that the cause of the cholestatic liver failure was secondary to bile canalicul disease due to the recurrence of aggressive HCV, bacterial cholangitis, drug toxicity, or a combination of these.

3.2. Survival Analysis. In this study, three patients are alive for more than 12 years after LT at the time of follow-up (15.0 years, 13.2 years, and 12.6 years). The Kaplan-Meier overall graft survival was one year 70.0%, five years 70.0%, and 10 years 70.0% (Figure 1(a)). The Kaplan-Meier overall patient survival was one year 88.9%, five years 77.8%, and 10 years 77.8% (Figure 1(b)).

3.3. Liver Biopsy Results and Management. The baseline 0-biopsy showed histological information of grafts, such as
the degree of ischemic change, fibrosis, and steatosis (Table 2). Four of nine HIV-1 infected patients experienced biopsy-confirmed acute cellular allograft rejection postoperatively (three mild rejections and one moderate acute rejection). Three patients (numbers 2, 5, and 9) received intravenous steroid cycle treatment and one patient (number 3) was treated with an increased dose of tacrolimus. Findings of postoperative liver biopsies are shown in Table 3. The long-term follow-up biopsies in patient number 1 (10 years and one month after LT) and patient number 3 (10 years and four months after LT) showed no signs of rejection or cirrhosis. The latest biopsy of patient number 4, five years after LT, showed advanced liver cirrhosis.

3.4. Postoperative Antiretroviral Therapy. The management of the antiretroviral therapy postoperatively was individualised, which was dependant on the medical condition/complication and drug resistance. The most recent anti-HIV regimen is shown in Table 3. Five of eight chronic HIV-1 infected patients (numbers 1, 6, 7, 8, and 9) had undetectable HIV RNA levels continuously during the entire follow-up. In three patients, the virus reappeared after LT (patients numbers 2, 4 and 5). Patient number 4 had undetectable HIV RNA before and after transplantation but the viral load increased to 1,980 copies/mL eight years and seven months after LT. He received RAL monotherapy but drug resistance for RAL was later confirmed. RAL was replaced by ABC, 3TC, and ZDV. Within two months the HIV RNA levels became undetectable. Later, the HIV RNA increased to 53 copies/mL at 10 years and thereafter became undetectable without modification of the treatment. All the living seven patients had undetectable HIV RNA at their latest evaluation. No patient developed AIDS syndrome after LT. Patient number 3 with PHI had received treatment with antiviral medication from day 8 after LT and HIV RNA became undetectable 4.5 months after LT. All patients except patient number 5 had CD4⁺ counts/μL > 100 during the whole follow-up period.

3.5. Treatment of the HCV Infection. The latest obtained HCV RNA is given in Table 3. Six patients were diagnosed with biopsy-confirmed recurrence of hepatitis C. Among them, three patients (patients numbers 1, 4, and 9) received peg-INF alpha-2a and ribavirin as previously described [10]. In two of these patients, patients numbers 1 and 4, HCV RNA became undetectable after treatment. Patient number 9 started treatment three months after LT with good efficacy. The remaining patients (numbers 6, 7 and 8) have relatively good liver function judged by laboratory tests, and are managed by minimising the immunosuppressive therapy. Another patient (number 5) was treated with INF due to increased HCV RNA without biopsy-confirmed hepatitis as described above. Patient number 4 had biopsy-confirmed advanced liver cirrhosis five years after LT, in spite of successful treatment for recurrence of hepatitis C. His liver function has been well compensated after the diagnosis up to the latest follow-up, 12.6 years after LT.

4. Discussion

HIV infection has generally been regarded as a contraindication for LT or at least experimental in the pre-HAART era. After introduction of HAART therapy, survival rates have improved also after LT in HIV-1 infected patients, as recently reported from several transplantation sites [13, 16, 17]. In our previous report on short-term outcome in HIV-infected patients after LT, we found that the replication of HIV-1 could effectively be inhibited with the antiretroviral therapy and that undetectable plasma HIV RNA levels were achieved in the majority of our patients. Hence, emergence of resistant HIV strains was only rarely seen [8]. In this long-term follow-up study, we confirm that the replication of HIV-1 can be effectively shut down by prolonged antiretroviral therapy when given in patients on continuous immunosuppressive therapy. HIV drug resistance was easily managed with altered HAART. No patient developed symptoms compatible with an AIDS diagnosis. The stable control of the HIV-1 infection and the adjustment of the immunosuppressive therapy, as well as the control of the HCV infection, resulted in good patient long-term survival. Hence, at least three patients are alive more than 12 years after LT (maximum 15.0 years), and
the five- and 10-year patient survival rate reached 77.8%. This result is better than the previously published data of long-term survival in patients with HIV transplanted for ESLD and is comparable to the LT outcome in monoinfected HCV patients transplanted for ESLD [18, 20].

As Neff et al. emphasised, it is important to recognise that not all patients with HIV and liver failure can be accepted for LT; thus, a careful selection of patients is mandatory [13]. When we reevaluated our two deceased patients, we found that they did not fully meet our principal criteria to be accepted for LT: one had high HIV-1 RNA (number 2) and the other low CD4+ counts (number 5). These two were accepted to the waiting list with adequate CD4+ counts, despite having too high HIV RNA levels. The low CD4+ counts in combination with low white blood cell counts in these patients were thought to be caused by increased consumption, due to portal hypertension and splenomegaly, and not from HIV induced immunosuppression. The decision to retransplant one patient six months after the initial LT, however, could be questioned since this patient’s CD4+ counts were below 100 during the whole post-LT period; furthermore, he had cholestatic liver failure without definitive identified cause. Probably, a high HIV RNA level is an important negative factor despite the presence of adequate CD4+ counts. Low CD4+ counts cannot be taken as less disadvantageous just because total white cell blood counts are low. Our second patient died three months after LT due to CNS failure without any clear cause and with a functioning liver graft. An episode of hypoglycemia was suspected but no hypoglycemic episode was recorded. Patient 5 died due to cholestatic liver failure. His liver biopsy result was not conclusive but liver failure caused by an advanced HCV relapse with fibrosing cholestatic hepatitis could not be ruled out. This patient’s clinical course has similarities to the clinical pattern as described by Norris et al.—rapid progression to cholestatic allograft dysfunction mainly as a consequence of HCV recurrence [14]. However, since this patient showed severe ischemia on the baseline 0-biopsy and since three arterial anastomoses were needed to reconstruct the arterial supply, we could not rule out surgical reasons for the negative outcome in the first graft [21]. The patient was retransplanted, although we suspected aggressive HCV recurrence as a possible reason. The almost identical outcome was seen after his retransplantation, indicating that recurrent cholestatic hepatitis was the main cause for the graft failure and patient’s death in this case. Although, the two patients we lost did not fully meet our eligibility criteria, none died from HIV-1 complications per se.

Acute cellular rejection was observed in four out of nine of our patients. This rate is compatible with other series of LTs at our and other institutes [17]. Three of four rejections were mild and no patient needed muromonab-CD3 (OKT3) or antithymoglobulin (ATG). Hence, acute rejections were managed in the same way as in non-HIV-1 infected patients. Significant interaction between PIs and calcineurin inhibitors was observed [9], but this interaction was easily handled during the long-term postoperative management. There is no definitive evidence that states what the best immunosuppression protocol in HIV-1-positive patients is. We switched calcineurin inhibitors from tacrolimus to cyclosporine in the last four patients since we traditionally use cyclosporine in HCV positive patients. We believe either drug may be used for HIV patients.

A major concern in HIV/HCV coinfected patients after LT is the faster and more aggressive course of the recurrent HCV infection [14]. It has been reported that the fibrosis scores were significantly higher in HIV/HCV coinfected patients than in HCV monoinfected patients 24 months after LT [16]. In our patients, four patients underwent IFN alpha therapy postoperatively. Three patients had good effect with the treatment and HCV RNA of two patients became undetectable [10]. In one patient, we could not change the clinical course of his cholestatic liver failure, neither during his first nor during his re-LT. Peg-IFN and ribavirin have so far been the standard treatment in this patient group, but no consensus exists about when to start the anti-HCV treatment after LT [19]. HCV RNA is universally detected after LT in these patients [17] but does not alone indicate the need to start anti-HCV treatment. Vernadakis et al. started peg-IFN and ribavirin postoperatively in all patients with preexisting HCV infection as soon as stable immunosuppression was obtained and after initiation of HAART [22]. The Miami group treated individual patient when needed [18]. Also, Norris et al. tried preemptive anti-HCV treatment in HIV patients but with no effect observed in two patients [14]. Our management is similar to that of the Miami group but more information and reports from other institutes are needed to clarify this.

Other studies have reported thrombotic complications such as arterial thrombosis as a significant problem in LT in HIV-1 infected patients [23]. However, in our study, we did not experience this complication. In these patients, standard postoperative thrombosis prophylaxis, with acetylsalicylic acid, seems sufficiently effective.

There are some limitations to this study. Firstly, we analysed a small series of patients; thus, we could not analyse prognostic factors on mortality. Secondly, there was no HIV-1 infected patient who underwent LT from November 2001 to November 2009. Nevertheless, we believe that the information on LT for HIV-1 with long-term evaluation should be shared with other transplantation centres. Out of our first five patients, four had HCV and HIV-1 infection second to previous treatment for hemophilia A and one due to PBC without i.v. drug use (IVDU); the following four patients had acquired their infection due to IVDU, which also may influence the long-term survival results.

To conclude, our experience suggests that LT is an effective life-saving procedure in selected HIV-1-positive patients, which offers long-term survival, at least for a selected subset, and at present there is no justification to exclude HIV-positive patients with ESLD from the waiting list for LT, provided that they have effective HAART treatment. Comorbidity such as HCV and the risk for recurrent drug abuse in affected patients may be of greater concern.

**Abbreviation**

LT: Liver transplantation
HIV-1: Human immunodeficiency virus type-1
HAART: Highly active antiretroviral therapy
AIDS: Acquired immune deficiency syndrome
HBV: Hepatitis B virus
HCV: Hepatitis C virus
ESLD: End-stage liver diseases
PBC: Primary biliary cirrhosis
ZDV: Zidovudine
3TC: Lamivudine
ABC: Abacavir
TDF: Tenofovir
NVP: Nevirapine
EFV: Efavirenz
NFV: Nelfinavir
LPV/r: Lopinavir/ritonavir
ENF: Enfurctivide
ATV: Atazanavir
d4T: Stavudine
ddi: Didanosine
RAL: Raltegravir
FTC: Emtricitabine
IFN: Interferon
PIs: Protease inhibitors
RAI: Rejection activity index
IVDU: Intravenous drug use.

Conflict of Interests
The authors of this paper have no conflict of interests to disclose.

References