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Liver transplantation in HIV patients: a case series from the Northeast region of Brazil

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ABSTRACT – Background – The emergence of potent combined highly active antiretroviral therapy (ART) in 1996 changed the natural history of HIV infection, with a significant reduction in mortality due to opportunistic infections but increased morbidity due to chronic cardiovascular, hepatic, and renal diseases. In May 2016, a reference center for liver transplantation in the Northeast of Brazil performed the first liver transplantations (LT) in HIV patients, with five others until 2021. **Methods –** The criteria for selection of LT were good adherence and absence of resistance to ART, HIV viral load maximum suppression, T-CD4+ lymphocyte count of more than 100 cells/mm^3, and absence of opportunistic infections in the last 6 months. **Results –** Six liver transplants were performed between May 2016 and May 2021, five men, with a mean age of 53.2 years, and one was a diabetic patient. All patients had access to grafts with short cold ischemia with a mean time of 5 hours and 39 minutes. The 4-month survival rate was 100%, with a range time of follow-up of 4-63 months (mean time of 31 months). The mean pre-transplant T-CD4+ lymphocyte count was 436 cells/mm^3. The mean length of hospital stay after transplantation was 16.8 days. One patient presented precocious vena cava thrombosis; another had stenosis of cavocaval anastomosis leading to refractory ascites, renal failure and post-transplant graft dysfunction, and another presented stenosis of choledochal anastomosis. Immunosuppression and prophylaxis were used according to standard protocols, and there were no differences in the profile of infections or rejection after liver transplantation. **Conclusion –** This case series documents good survival and usual transplant procedures for confirmed HIV cases.

Keywords – Liver transplantation; HIV.

INTRODUCTION

The emergence of the potent combined highly active antiretroviral therapy (ART) in 1996 dramatically changed the natural history of HIV infection, significantly reducing mortality due to opportunistic infections. However, an increased incidence of morbidity due to chronic cardiovascular, hepatic, and renal diseases was observed[1]. The significant improvement in survival and quality of life that ART brought to this population made possible the access of HIV patients to almost all types of treatments performed in the general population, including liver transplantation (LT)[2].

A growing number of liver transplants in HIV patients has been performed with promising results, even in patients with hepatocellular carcinoma (HCC) and hepatitis C virus (HCV) co-infection[3], and the survival of HIV-HCV coinfected recipients has improved after the advent of direct-acting antiviral drugs (DAA). The consensus of the American Liver Transplant Association recently reviewed the worldwide experience in this subgroup of patients corroborating a similar survival to the general population[2].

The Liver Transplant Service of the Walter Cantídio University Hospital, Federal University of Ceará, Fortaleza, Ceará, Brazil, performed the first LT in May 2002. In August 2021, the service reached a total of 2,000 transplants. The first LT in an HIV patient was carried out in this service in May 2016. Until May 2021, five more LT in HIV patients were performed and motivated the authors to describe this experience.

METHODS

This case series is a retrospective observational study with data collection from medical records. Selection criteria for indication of LT followed the guidelines corroborated by the recent consensus of the American Liver Transplant Society[2]. HIV patients with good adherence and absence of resistance to ART, undetectable HIV viral load, and T-CD4+ lymphocytes count ≥100 cells/mm^3, with no evidence of opportunistic infections in the last 6 months or opportunistic neoplasms, were accepted. Patients with severe toxicity due to ART, unable to maintain antiretroviral use, but with controlled disease and no evidence of resistance to ART were also accepted.

The ART used by the transplanted patients in this service was adequate before the transplant with the exchange of medications with an unfavorable interaction profile with immunosuppressants. All patients were transplanted using triple ART containing

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dolutegravir and tenofovir. The third ART drug was lamivudine, abacavir, and zidovudine in four, one, and one patient, respectively.

The prophylaxis of bacterial and opportunistic infections performed in this subgroup of patients followed the standard protocol: sulfamethoxazole/trimethoprim (400/80 mg) in the first sixth months for preventing Pneumocystis jiroveci, isoniazid (300 mg) for 6 months for patients with tuberculin skin test (TST) ≥5 mm, and nystatin oral solution (5 mL) 4 times a day in the first three months for prophylaxis of mucosal fungal infection. Cytomegalovirus (CMV) prophylaxis is only done if the donor is seropositive and the recipient is seronegative. Surveillance for CMV infection is performed with PCR quantification every 15 days. Treatment is instituted preemptively in symptomatic patients with PCR >2000 IU/mL and in asymptomatic patients with PCR >5000 IU/mL, with intravenous Ganciclovir 5 mg/kg every 12 hours oral Valganciclovir 900 mg every 12 hours for a minimum of 3 weeks.

Immunosuppression performed followed the standard protocol, consisting of tacrolimus 0.1 mg/kg/day and hydrocortisone 100 mg IV 12/12 h converted to prednisone 20 mg/day for the first month, 15 mg for the second month, 10 mg for the third month, and 5 mg for the fourth to the 6 month of transplantation.

RESULTS

All six patients had undetectable HIV viral load prior to surgery. The mean pre-transplant T-CD4+ lymphocyte cell count was 436 cells/mm^3 (Δ153 to 861). The mean age was 53.2 years (Δ44 to 60). Five men. Two patients required LT due to alcoholic cirrhosis, two due to HCC and hepatitis C infection, one due to fulminant hepatitis, probably caused by the use of ART or isoniazid for treatment of latent tuberculosis, and the other due to nonalcoholic fatty liver disease (NAFLD). One patient had diabetes, and the other had systemic arterial hypertension and chronic kidney disease not requiring dialysis.

Both patients with hepatitis C and HCC had been cured of hepatitis C infection before transplantation. One of them had successfully performed two transarterial chemoembolization (TACE) sessions on the HCC nodules in the liver with downstaging success. In the explant, this HCC patient presented a microscopic neurovascular invasion. The patient who was transplanted for fulminant hepatitis after starting ART and isoniazid to treat latent tuberculosis had cirrhosis with a biliary pattern in the explant. One of the patients who was transplanted due to alcoholic cirrhosis also had a biliary pattern in the explant. Only one patient who was transplanted for alcoholic cirrhosis had a history of opportunistic infection (esophageal candidiasis) more than 6 months before transplantation. No patient had portal thrombosis in the preoperative evaluation phase.

All patients underwent LT with the Piggyback technique and end-to-end anastomosis of the portal vein and common bile duct. The mean time of cold and hot ischemia was 5 hours and 39 minutes (Δ4h and 5 min to 7 h and 51 min) and 31.3 minutes (Δ24 to 37), respectively. Only one patient received two red cells and two units of fresh frozen plasma.

Transplanted livers were all biopsied at the time of surgery and were considered suitable, presenting less than 5% steatosis and mild or absence of fibrosis.

One patient with alcoholic cirrhosis used meropenem for seven days after LT due to a prior infection in the donor. The patient with fulminant hepatitis who was hospitalized for more than 15 days received prophylaxis with piperacillin/tazobactam plus vancomycin and fluconazole for 7, 7 and 14 days, respectively. The patient with NAFLD used vancomycin plus meropenem and piperacillin/tazobactam during the hospital stay.

The mean hospitalization time was 16.8 days varying from 9 to 29 days. The average length of hospital stay in liver transplant patients this service is 8 days.

The patient who was hospitalized for the longest time presented inferior vena cava thrombosis with difficult-to-control ascites, and was anticoagulated with warfarin. The patient with nonalcoholic fatty liver disease (NAFLD) had stenosis of the anastomosis of the choledochal duct, requiring endoscopic retrograde cholangiopancreatography. Another patient had cavocaval anastomosis stenosis, leading to refractory ascites, requiring weekly relief paracentesis and realization of percutaneous dilation, with clinical improvement. This patient also had dialytic renal failure and required hospital admission two months after the transplant due to obstruction of the venous dialysis catheter. This patient also presented graft dysfunction. No other patient presented graft dysfunction or other surgical complications.

Three patients who had non-dialytic early renal dysfunction received reduced doses of tacrolimus associated with mycophenolate sodium (two patients) or everolimus (one patient). No patient presented rejection frames.

ART was well tolerated in all patients, and it was not necessary to change medications after LT. One patient had a surgical wound infection and subsequent recurrent urinary tract infections. No patient has had any opportunistic infection or CMV reactivation so far. To this date, all patients are alive with a follow-up time ranging from 4 to 63 months (mean time of 31 months). TABLE 1 summarizes important patient data.

TABLE 1. Patients' data summary.

Patient	1	2	3	4	5	6
Transplant causes	HCC + hepatitis C	Alcoholic cirrhosis	Alcoholic cirrhosis	Fulminant hepatitis	HCC+ hepatitis C	NASH
Pre-transplant MELD	8	23	21	33	24	21
Hospital stay time	9 days	10 days	29 days	11 days	15 days	21 days
Surgical complications	Surgical wound infection	No	Thrombosis of proximal vena cava	No	Cavocaval anastomosis stenosis	Choledocal anastomosis stenosis
Post-transplant follow-up time (months)	63	39	36	36	9	4

HCC: Hepatocellular carcinoma; NASH: Nonalcoholic fatty liver disease.

DISCUSSION

In our sample of HIV patients undergoing LT, the patients were relatively young, with no relevant comorbidities or prior thromboses, and had access to suitable donors with short cold ischemia time; fears of a higher incidence of infections were not confirmed, and opportunistic infections were not detected. This profile of patients certainly contributed to the survival rate in our service. Our findings were similar to those of other studies with HIV carriers undergoing LT[2].

The mean hospitalization time after LT in HIV carriers (16.8 days) was longer than the average of this service, which varies from seven to ten days (mean 8 days).

The risk factors associated with shorter post-transplant survival in HIV-positive patients were higher MELD and lower BMI- reflecting sarcopenia - which is similar to HIV-negative patients[4]. The MELD in this series varied from 8 to 33.

It is necessary to attain thorough social and behavioral analysis regarding alcohol and illicit drugs abstinence, psychological stability, and family support in HIV patients who may receive LT[5,6].

In the post-transplant, monitoring the immunosuppression and ART and opportunistic infection prophylaxis is essential. HIV-infected patients' post-transplant prophylaxis is similar to the other post-transplant patients. Besides conventional post-transplant prophylaxis for Pneumocystis jiroveci, these patients must receive prophylaxis for other agents depending on epidemiological precedents. For instance, patients with TST ≥5 mm or in contact with patients with bacilliferous tuberculosis must receive treatment for latent tuberculosis[7].

The good immunological profile of this case series and the good adherence to standard prophylaxis allowed the absence of any opportunistic infection. Contrary to what some authors have suggested, we have not documented any rejection phenomenon in these cases[2].

These patients also present a higher risk of arterial and venous thromboembolism of uncertain etiology. Venous thromboembolism occurs ten times more frequently in these patients when compared to the general population. This can be explained due to HIV-related pro-thrombotic alterations, such as hyperplasia of the intimal and smooth muscle layer of vessels, associated with perivascular infiltrates, increased adhesion molecules in the endothelium and non-specific vasculitis. In addition, ART has been linked to increased inflammation, atherosclerotic progression, and vascular destabilization that precedes thrombosis. In a single center study with HIV patients who underwent LT, thrombotic complications occurred in 33% of the sample. This draws attention to the need for anti-thrombotic chemoprophylaxis in these patients. In our series, one patient developed thrombotic surgical complications[7,8].

A subgroup that deserves to be highlighted is patients coinfected with hepatitis B or C. These patients have higher risks of cirrhosis progression, HCC and terminal hepatic disease than the mono-infected[9]. Historically, the coinfected patients with hepatitis C had a worse prognosis because the immunosuppression frequently resulted in infectious complications and aggressive recurrence of the virus C, which is the leading cause of death in these patients. The use of ART, the recent advances in hepatitis C treatment (direct-acting antiviral - DAA drugs), and the opportunistic infections prophylaxis potentialized these patients' survival, and the elimination of the virus C drastically increases survival, as demonstrated in recent studies[10,11]. In this series, both patients coinfected with hepatitis C had already cured hepatitis before transplantation, not influencing the post-LT outcome.

Although one patient had undifferentiated HCC and angiolymphatic invasion in the explant, there was no recurrence at 33 months of follow-up. The incidence of HCC increased progressively in the last decades in HIV patients, being responsible for up to 40% of hepatic disease-related death in this population. It has been suggested that the HCC has a faster progression in these patients, leading to worse outcomes. The data regarding survival and post-transplant HCC recurrence is controversial. A multicenter cohort study with 271 HIV-positive patients who underwent LT and 811 HIV-negative patients control group demonstrated that survival and recurrence were similar in both groups. These results are satisfactory, allowing the recommendation of considering HIV-positive patients with early stages of HCC as adequate candidates for LT[12].

Studies have shown that solid organ transplantation can be considered a standard treatment for end-organ-disease, with excellent and increased over-time survival, and that pre and post-transplant outcomes for liver transplantation can be improved by partnerships between the transplant team and infectious disease physicians, allowing adequate opportunistic infections prophylaxis, HCV co-infection treatment and ART, reducing drug interactions[4,13-15].

Therefore, studies have demonstrated good post-transplant results in HIV-positive patients, including the coinfected hepatitis B and C and HCC subgroups. Two patients were transplanted due to HCC and hepatitis C, with good outcomes in our series. Hopefully, documenting the survival of HIV patients transplanted at this service can encourage other services to include these patients in their LT lists.

CONCLUSION

This case series documents good survival and usual transplant procedures and complications for confirmed HIV cases.

Authors' contribution

Hyppolito EB: conception, statistical analysis, text writing and review, data collection, patients' follow-up. Castro AR: text writing and review, data collection, submission. Girão ES, Coêlho GR and Garcia JHP: text review, patients' follow-up. Pires Neto RJ: text writing and review.

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RESUMO – Contexto – A emergência da terapia antirretroviral de alta potência, em 1996, mudou a história natural da infecção por HIV, com redução significativa de mortalidade por infecções oportunistas, mas com aumento de morbidade por doenças crônicas cardiovasculares, hepáticas e renais. Em maio de 2016, um centro de referência em transplante hepático no Nordeste do Brasil realizou o primeiro transplante hepático em portadores de HIV, com cinco outros até 2021. **Métodos –** Os critérios de seleção para o transplante hepático foram: boa aderência e ausência de resistência à terapia antirretroviral, carga viral indetectável, contagem de linfócitos T-CD4+ acima de 100/ mm^3 e ausência de infecções oportunistas nos últimos 6 meses. **Resultados –** Seis transplantes hepáticos foram feitos em portadores de HIV entre maio de 2016 e maio de 2021, cinco homens, com idade média de 53,2 anos, um paciente diabético. Todos os pacientes tiveram acesso a enxertos com tempo de isquemia fria curto com média de 5 horas e 39 minutos. A sobrevida em 4 meses foi de 100%, com tempo de acompanhamento de 4-63 meses (média de 31 meses). A contagem média de linfócitos T-CD4+ pré-transplante foi de 436 células/ mm^3. A média de tempo de internação foi de 16,8 dias. Um paciente teve trombose de veia cava proximal; outro teve estenose de anastomose cavo-caval, levando à ascite refratária, falência renal e disfunção de enxerto pós-transplante; e outro teve estenose de anastomose do colédoco. A imunossupressão e a profilaxia foram usadas de acordo com protocolos padrão e não houve diferenças no perfil de infecções ou de rejeição pós-transplante. **Conclusão –** Esta casuística ilustra que o transplante de fígado em portadores do HIV apresenta complicações usuais e sobrevida satisfatória.

Palavras-chave – Transplante de fígado; HIV.

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