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TOPIC HIGHLIGHT

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Pros and cons of liver transplantation in human immunodeficiency virus infected recipients

Umberto Baccarani, Elda Righi, Gian Luigi Adani, Dario Lorenzin, Alberto Pasqualucci, Matteo Bassetti, Andrea Risaliti

Umberto Baccarani, Gian Luigi Adani, Dario Lorenzin, Andrea Risaliti, Liver Transplant Unit, Department of Medical and Biological Sciences, University Hospital of Udine, 33100 Udine, Italy
Elda Righi, Matteo Bassetti, Division of Infectious Disease, University Hospital of Udine, 33100 Udine, Italy
Alberto Pasqualucci, Department of Anaesthesiology, University of Perugia, 33100 Udine, Italy
Author contributions: Baccarani U and Righi E equally contributed to conception and design, acquisition of data, or analysis and interpretation of data, drafted and revised the article critically for important intellectual content; Adani GL and Lorenzin D made substantial contributions to acquisition of data or analysis and interpretation; Pasqualucci A, Bassetti M and Risaliti A made final approval of the version to be published.
Correspondence to: Umberto Baccarani, MD, PhD, FEBS, Liver Transplant Unit, Department of Medical and Biological Sciences, University Hospital of Udine, P.le S.M. della Misericordia 15, Pad. Petracco, 33100 Udine, Italy. umberto.baccarani@uniud.it
Telephone: +39-432-559902 Fax: +39-432-559552
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Abstract

Before the introduction of combined highly active antiretroviral therapy, a positive human immunodeficiency virus (HIV) serological status represented an absolute contraindication for solid organ transplant (SOT). The advent of highly effective combined antiretroviral therapy in 1996 largely contributed to the increased demand for SOT in HIV-positive individuals due to increased patients' life expectancy associated with the increasing prevalence of end-stage liver disease (ESLD). Nowadays, liver failure represents a frequent cause of mortality in the HIV-infected population mainly due to coinfection with hepatitis viruses sharing the same way of transmission. Thus, liver transplantation (LT) represents a reasonable approach in HIV patients with stable infection and ESLD. Available data presently supports with good evidence the practice of LT in the HIV-positive population. Thus, the issue is no longer "whether it is correct to transplant HIV-infected patients", but "who are the patients who can be safely transplanted" and "when is the best time to perform LT". Indeed, the benefits of LT in HIV-infected patients, especially in terms of mid- and long-term patient and graft survivals, are strictly related to the patients' selection and to the correct timing for transplantation, especially when hepatitis C virus coinfection is present. Aim of this article is to review the pros and cons of LT in the cohort of HIV infected recipients.

Key words: Liver transplantation; Human immunodeficiency virus/hepatitis C virus coinfection; Hepatocellular carcinoma; Immunosuppression

Core tip: This article reviews the most recent literature in the field of liver transplantation in human immunodeficiency virus (HIV) positive recipients with special focus on hepatitis C virus/HIV coinfection and hepatocellular carcinoma in HIV recipients. This field of research is one of the most intriguing up to now since end-stage liver disease has become the first cause of death in HIV patients and the request for liver transplantation in this subgroup of HIV positive patients is going to increase over time.

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CHANGE IN THE EPIDEMIOLOGY OF HIV-INFECTION IN THE COMBINED ANTIRETROVIRAL THERAPY ERA

Before the introduction of combined antiretroviral therapy (C-ART), a positive human immunodeficiency virus (HIV) serological status represented an absolute contraindication for solid organ transplant (SOT)[1-3]. The advent of highly effective C-ART in 1996 largely contributed to the increased demand for SOT in HIV-positive individuals due to increased patients' life expectancy[4-7] associated with the increasing prevalence of end-stage liver (ESLD) and renal diseases (ESRD)[8-10]. Before C-ART, factors endangering a positive outcome for SOT in HIV-positive recipients included the high immunosuppression (*i.e.*, combination of low absolute CD4 T cell count and post-transplant immunosuppressants), reduced life expectancy, and the occurrence of life-threatening opportunistic infections (OI). Studies from the past decade have shown that HIV-infected patients with T lymphocyte reconstitution on stable C-ART have mortality rates similar to the general population and rare occurrence of neoplasms and OI[3,6]. Nevertheless, HIV infection in the form of a chronic illness with increased life expectancy in association with a prolonged use of potentially toxic drugs can lead, with time, to organ deterioration. Nowadays, hepatic and renal failures represent frequent causes of morbidity in the HIV-infected population. Thus, SOT represents a reasonable approach in HIV patients with stable infection and end-stage organ disease. Among SOT, kidney transplantation proved to be a valid therapeutic approach in HIV-infected patients, displaying higher survival rates compared to patients remaining on dialysis[11,12]. A recent prospective study encompassing 150 kidney-transplant (KT) recipients in an HIV cohort reported survival rates of 94.6% and 88.2% at one and 3 years post-transplantation, respectively[12]. Although simultaneous pancreas-kidney transplant (SPK) represents the only proven long-term therapeutic approach for diabetic patients having progressed to ESRD, the incidence of surgical complications remains high and represents a major limiting factor to endorsement in HIV-positive recipients, and only few cases have been reported in literature[13]. Nowadays, liver transplant (LT) still poses a few challenges for HIV recipients, showing high mortality rates among HIV/hepatitis C virus (HCV) coinfected patients[14]. Limited data is available for lung and heart transplants in HIV-positive recipients; in these instances, a careful patient selection and follow-up are mandatory.

INCLUSION CRITERIA FOR LIVER TRANSPLANTATION IN HIV-POSITIVE PATIENTS

Immunovirological parameters and choice of post-LT C-ART are important elements to screen and monitor in HIV-positive patients candidate to receive LT. Ragni *et al*[15] identified, besides HCV-HIV coinfection, specific HIV-related factors (*i.e.*, post-LT C-ART tolerance and CD4 T-cell absolute number) as predictors of mortality in LT at univariate analysis. Overall, inclusion criteria regarding liver status are identical in HIV-positive and HIV-negative patients. No heroin or cocaine abuse has to be documented in the past two years and absence of alcohol abuse for at least six months is necessary for inclusion in the transplant waiting list. OI that are still active or not controlled by therapy (*i.e.*, progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis), neoplasms for which an adequate disease-free period has not been documented, chronic wasting syndrome, and severe malnutrition represent contraindications for SOT. A stable (for more than six months) absolute number of CD4 T cell above 200 cells/mmc and an undetectable viral load are required if the patient is on C-ART and has had a previous history of OI (*i.e.*, adequately treated tuberculosis, candidiasis, pneumocystosis). Exceptions are represented by patients who present lower absolute CD4 T cell count (*i.e.*, between 100 and 200 cells/mmc, potentially related to hypersplenism) but have no history of OI, or patients who cannot receive antiretrovirals due to severe liver impairment. In the latter case, previous documentation of therapeutic efficacy and/or genotypic or phenotypic tests documenting the availability of an effective C-ART that can achieve undetectable viral load is required. In all cases, proof of strict compliance to the prescribed therapy and to the post-LT follow up have to be documented. Selection criteria for LT in HIV-positive recipients are summarized in Table 1. Most Centers refer to the criteria set by the American Society of Transplantation (AST), although slightly differences in the inclusion criteria have been reported between the United States and across Europe[16]. For example, a one-year OI free is required in Italy in case of previous OI, while in the United Kingdom the absence of OI after the introduction of an effective C-ART has to be documented[17,18].

Timing of liver transplantation and graft availability

Once established that a number of HIV-infected patients can afford LT with a reasonably high expected benefit on survival, the next challenge is to determine the best timing of the procedure. In preliminary studies, Ragni *et al*[15] demonstrated significantly shorter pre-transplantation survival, mainly due to infections, in HIV-infected patients listed for liver transplantation when compared with HIV-negative patients, despite equivalent MELD scores at the time of listing. In another study, Stock *et al*[19] reported that MELD score did not accurately predict survival of HIV/HCV coinfected patients on waiting list for LT. Moreover, survival rates of HIV-infected patients with decompensated cirrhosis are significantly shorter than in HIV-negative patients. Pineda *et al*[20] demonstrated in a multicentre Spanish case-control study that the outcome of cirrhosis after the first decompensation in HIV/HCV coinfected patients is much worse than that observed in the monoinfected HCV-positive population. Specifically, survival rates at 1, 2, and 5 years for HIV/

Table 1 Inclusion criteria for liver transplantation in human immunodeficiency virus - positive patients

Absolute CD4 T cell count above 200 cells/mmc, if history of opportunistic infections or AIDS-defining malignancies	Progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis (> 1 mo duration)
Absolute CD4 T cell count above 100 cells/mmc if absence of previous documented opportunistic infections	Lymphoma or other neoplasms, unless an adequate disease-free period is documented
Undetectable HIV-RNA in blood for patients on C-ART; if not on C-ART, previous documentation of efficacious therapy or genotypic/phenotypic resistance test documenting available post-LT C-ART options	
No active (< 1 yr) opportunistic infections, no wasting syndrome or severe malnutrition	
Compliance to therapies and to follow-up visits	

LT: Liver transplantation; C-ART: Combined antiretroviral therapy; HIV: Human immunodeficiency virus.

HCV co-infected and HCV monoinfected populations were 54% *vs* 74%, 40% *vs* 61%, and 25% *vs* 44%, respectively. More recently, Duclos-Vallée *et al*[21] have shown that a high MELD score ($P = 0.03$; RR = 1.08; 95%CI) at the time of transplantation may predict a poor outcome in HIV-infected LT recipients. Taken together, this data suggests that HIV-infected patients reaching the minimal MELD score requested for inclusion on the waiting list (≥ 15) should be listed and transplanted as soon as possible. Murillas *et al*[22] showed how the mortality rate for a given MELD score in HIV-infected patients was similar to the mortality rate in non-HIV infected patients with a MELD score that was roughly 10 points higher. Also, the MELD score correlated with death on the waiting list for the HIV-infected patients and the absolute value of the MELD score was associated with significantly poorer survival rates in comparison with HIV-negative monoinfected patients. In conclusion, the authors suggest that some prioritization for HIV-positive recipients might be indicated on the basis of these findings. Although this data hints that the MELD score in HIV-positive candidate to LT may underestimate the progression of liver disease, a reconsideration of the MELD scoring system specific for HIV-positive recipients does not seem feasible taken the shortage of organ donors. Thus, a more likely strategy to decrease waiting list mortality and improve the chances for getting a liver transplant for HIV/HCV coinfected recipients would be to pursue alternative sources of liver donors that would facilitate earlier transplantation. Nevertheless, the importance of early referral of the HIV/HCV coinfected patient for liver transplant evaluation remains a cornerstone in the management of these patients. In the absence of additional MELD points to obtain liver transplants at the lower "true" MELD score, the ability to achieve an earlier transplant (at a lower MELD score) can generally be achieved by 3 strategies.

The three strategies including: (1) Utilization of living donor liver grafts (usually right lobe donors). Clearly, the major advantage of providing a donor liver at a lower MELD score to the HIV-positive recipient must be weighted against the morbidity to the living donor as well as the increased risk of biliary tract complications and hepatic artery thrombosis in the recipient[23]. In addition to the informed consent regarding the rates of morbidity and mortality associated with donating a right lobe, the donor should be informed of the current outcomes in HIV-coinfected patients; (2) Utilization of high risk donors (*i.e.*, negative at HIV antibody testing but potentially within the window period between infection and seroconversion due to high behavioral risks[24]). As the availability of serologically negative, high-infectious-risk donors has decreased, there have been extensive discussions regarding the potential use of HIV-positive deceased donors for HIV-positive recipients. Results from a limited cohort of HIV-positive kidney donors seemed promising[25]; the cautious use of HIV-positive deceased donors whose immunological, virological, and C-ART history has been documented would be a potential alternative source of deceased liver donors; and (3) Utilization of deceased donor organs considered to be at a higher risk for early allograft dysfunction, such as older donors, liver donors with significant macrovescicular fat, and non-heart-beating donors. However, the use of this category of so called "extended criteria" donors for HIV-infected recipients may be hampered by a higher risk of early or late graft loss especially in HIV/HCV coinfected patients. The poorer outcomes with extended criteria donors undoubtedly reflect the management complexities following transplantation in the coinfected recipients and their relative inability to tolerate the insult of early graft dysfunction[26].

In conclusion, due to the extremely high mortality rates in HIV-coinfected patients after their first liver disease clinical decompensation, only a small percentage of HIV-infected patients can be actually considered adequate candidates for LT. Furthermore, for the few patients accepted for LT, a high mortality rate on the waiting list reduces the probability of receiving a transplant[22]. These findings highlight the importance of early referral along with multidisciplinary care to expand the number of HIV-positive patients with end-stage liver disease who could be candidates for successful LT and minimize the number of deaths on the waiting lists. Moreover, in an era of donor's organs shortage pursuing alternative sources of livers, such as living donation and extended criteria or high risk donors, might be encouraged in order to expand the possibility of liver transplantation in HIV infected patients without hampering non-HIV candidates.

Surgical challenges of liver transplantation in HIV recipients

Surgical liver transplantation techniques in HIV-positive are not different compared to the procedures undertaken in non-HIV recipients. In some centers, the wide-

Table 2 Factors correlated with mortality and graft loss in human immunodeficiency virus/hepatitis C virus-positive recipients of liver transplantation[14]

Follow-up at 3 yr post-LT	HIV/HIV (89)	HCV (235)	*P* value
Patient survival (%)	60	79	< 0.001
Graft survival (%)	53	74	< 0.001
Acute rejection (%)	39	24	0.02
Severe HCV reinfection (%)	29	23	0.21

LT: Liver transplantation; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

spread use of these procedures has been hampered by the surgeons' fear to get in contact with HIV recipients contaminated blood. The reasons for a low risk of HIV transmission from the surgical team are readily available and include routine utilization of sterile surgical technique and universal precautions. The surgical team is continually aware of the dangers of transmission of infections, which is inclusive of, but not limited to, HIV infection. In addition, we now know that the blood concentration of viral particles in patients who are infected with HIV is low, especially since the majority of the patients have negative pre-transplant viremia. In the event of a high-risk exposure during surgical procedures, the CDC recommends post-exposure antiretroviral chemoprophylaxis. There is statistical evidence that indicates possible prevention of occupational infection, which has been observed from hollow needle stick exposures and has been extrapolated to have potential benefits following solid needle and other percutaneous or mucous membrane exposures. Surgical practices regarding HIV-positive patients have been summarized in the 2004 Bulletin of the American College of Surgeons[27].

LIVER TRANSPLANTATION FOR HIV/HCV COINFECTION

After the introduction of C-ART, a dramatic decrease in OI and an increase in non-OI diseases have been registered. Specifically, liver disease currently is the most common non-AIDS-related cause of death, accounting for up to 18%[28]. Due to similar risk factors for disease transmission, HIV infected patients often has HCV coinfection. Data reports HIV/HCV coinfection rates in around one third of patients, with rates that can reach up to 70% in patients progressing to cirrhosis. HIV/HCV coinfection is known to significantly impact the progression of HCV-related hepatopathy towards cirrhosis, liver failure, and hepatocellular carcinoma (HCC)[29]. Furthermore, antiretrovirals may contribute to hepatotoxicity along with alcohol consumption and non-alcoholic steatosis[30,31]. Often, indication to LT in HIV-positive patients is represented by liver impairment (recurrent ascites, portosystemic encepalopathy, esophageal varices rupture) or HCC[32]. Due to severe conditions and high mortality rates in coinfected HIV/HCV patients with advanced liver disease, an accurate selection of transplant recipients is mandatory. Predictors of mortality in HIV-infected patients with HCV-related ESLD after the first hepatic decompensation include a Child-Pugh score $\geqslant$ 10, the presence of encephalopathy, a low absolute CD4 T cell count, and absence of C-ART[33]. Although excellent results have been reported in monoinfected HIV patients undergoing LT, mortality in HIV/HCV patients remains high at 1, 3, and 5 years compared to monoinfected HCV LT recipients (74%, 61%, and 44% *vs* 54%, 40%, and 25%, respectively), mainly due to high rates of severe HCV post-LT reinfection, including fibrosing cholestatic forms[34]. As summarized in Table 2, Terrault *et al*[35] confirmed significantly higher rates of mortality, graft loss, and acute rejection in coinfected HIV/HCV subjects compared to HCV monoinfected patients. Overall, Miro *et al*[14] showed mortality rates around 55% in 84 HIV/HCV LT recipients at 5 years post-LT. Terrault *et al*[35] showed that the subgroup of HIV/HCV patients with no risk factors (*i.e.*, old age or HCV-positive donor, low BMI) had mortality rates comparable to controls. Furthermore, HIV/HCV positive patients displayed rates of severe HCV reinfection at 3 years post-LT similar to monoinfected HCV-positive recipients. This suggests how HIV/HCV coinfection *per se* does not represent an absolute contraindication for LT; nonetheless, a thorough selection of recipients has to be made, evaluating attentively all the risk factors that can lead to an unfavourable outcome. Although further studies on a large scale are required, risk factors for mortality and graft failure in HIV/HCV recipients of LT have been identified (Table 3)[14]. Interestingly, among the risk factors the performance of a limited number of LT at a transplantation Center represents a risk factor correlated to an increased mortality in HIV-positive recipients, probably because of a lack of expertise in managing HIV-positive recipients[14]. Furthermore, the presence of experts in HIV medicine (*i.e.*, virological and immunological follow-up, C-ART, drug-to-drug interactions, *etc.*) and availability of laboratory tests specific for HIV infection (*i.e.*, HIV-RNA, HCV-RNA, CD4 T cell count) are mandatory for a correct management of these patients. Moreno *et al*[36] demonstrated that the occurrence of previous OI correlated with a high number of post-LT infections, suggesting that the history of OI should be carefully investigated during pre-transplant selection. Due to organ shortage and limited data, liver re-transplantation has been debated in HIV-positive recipients. A study encompassing 14 re-OLT HIV-positive recipients from a Spanish cohort (6% retransplantation rate) showed a survival probability of 42% at 3 years (compared to 64% among controls, difference not significant). Factors correlated with better outcomes were HCV-RNA negativity at re-transplant and late (> 30 d from the first LT) graft failure[37].

Table 3 Factors predictive of mortality and graft failure at multivariate analysis in human immunodeficiency virus/hepatitis C virus recipients of liver transplantation

Mortality	HR (95%CI), *P* value	Graft loss	HR (95%CI), *P* value
HIV infection[14,35]	2.3 (1.3–3.8), 0.0002	BMI < 21[35]	3.2 (1.3–7.7), 0.01
HCV genotype 1[14]	2.14 (1.24–3.41), 0.006	Donor age by decade[35]	1.3 (1.0–1.6), 0.04
Donor index risk[35]	3.03 (1.57–5.83), 0.001	HCV-positive donor[35]	2.5 (1.1–5.6), 0.03
		Combined kidney-LT[35]	3.8 (1.6–9.1), 0.003
		MELD score[14]	1.06 (1.01–1.11), 0.023
		Centers performing < 1 LT/yr[14]	2.82 (1.30–6.94), 0.009
		Treated acute rejection1[35]	2.0 (1.0–4.0), 0.06
		HIV infection[35]	1.9 (1.2–3.1), 0.01

[1]In HIV-positive individuals with or without HCV. HCV: Hepatitis C virus; BMI: Body mass index; LT: Liver transplantation; HIV: Human immunodeficiency virus.

LIVER TRANSPLANTATION IN HIV RECIPIENTS NOT COINFECTED WITH HCV

HIV/hepatitis B virus (HBV)-coinfected LT recipients seem to have better outcomes compared with those in HIV/HCV-coinfected liver transplant recipients as long as they receive early referral for LT and treatment of lamivudine-resistant HBV infection after LT[21,38-40]. In the absence of HCV, among those with HBV infection, those with HIV coinfection had a higher rate of death (0.14 per person-year) than those without HIV infection (0.06 per person-year), but this difference was not statistically significant (P = 0.18). There was also no significant difference in death rates between HIV(+) patients without coinfection [HIV(+)/HBsAg(-)/HCVAb(-)] and HIV/HBV-coinfected patients [HIV(+)/HBsAg(+)/HCVAb(-)] patients (P = 0.10). Univariate analysis also showed that the estimated 2 and 3-year survival probabilities of HIV-infected patients were lower than that of non-HIV patients. However, this excess risk appeared entirely among those with coinfections, as none of the 24 HIV(+) patients who did not have HBV or HCV died during follow-up. These results should be interpreted with caution because the number of HIV/HBV-coinfected patients was too small in the database analyzed, however the results from this large retrospective National database[40] analysis were similar to those found by other investigators[41,42].

Liver transplantation for HCC and HIV

HCC is the leading cause of death among patients with liver cirrhosis and is the fifth most frequent malignant tumor worldwide[43]. The most common underlying diseases to this condition are chronic viral hepatitis and alcohol abuse. These conditions are epidemiologically linked with HIV infection, sharing common behavioral risk factors[44]. Several reports have outlined a more aggressive course of HCC in HIV infected patients[45,46]. HIV, *per se*, can boost carcinogenesis with the pivotal role of the HIV-tat protein inducing growth signals and enhancing HCC cell proliferation and antitumor immune response[47]. Liver transplantation (LT) in patients with HIV and ESLD is a recent indication and it is still a matter of debate in case of HCC. Only few studies reported so far on that issue. The multicenter comparative study by Di Benedetto *et al*[48] reported 155 patients with ESLD underwent LT for HCC; among them, 30 patients were HIV-infected. The dropout rate between the two groups was comparable and it was reported as 26% and 24%, respectively, in HIV infected and -uninfected patients (P = 0.99). In HIV-infected and -uninfected individuals, the HCC recurrence rates were 6.7% (2 out of 30 patients) and 14.4% (18 out of 125 patients), respectively (P = 0.15). One- and 3-year HCC-disease-free survival for patients with and without HIV infection was 100% and 95.2% and 91.4% and 83.6%, respectively (P = 0.32). Vibert *et al*[49] compared two population of HCC patients, one HIV+ and the other HIV-, listed for LT and reported that because of a higher dropout rate among HIV+ patients, HIV infection impaired the results of LT for HCC on an intent-to-treat basis but had no significant impact on overall survival (OS) and recurrence free survival (RFS) after LT. Differently from Vibert *et al*[49], in our personal series[50] of 13 LT for HCC in HIV+, we do not have any drop-out and none of the transplanted patients experienced HCC recurrence although 23% were outside the Milan criteria but only 7.7.% had microvascular invasion at explants, while in the French cohort microvascular invasion was present in 50% of cases. Comparison of the results of LT for HCC in HIV+ *vs* HIV- recipients reported in the literature is shown in Table 4 and none of the parameters included showed a statistical significant difference.

Immunosuppression and C-ART in HIV-positive liver transplanted patients

The immunosuppressive regimen after LT in an HIV infected recipient does not differ from the one normally utilized in non-HIV patients and it is usually based on calcineurin inhibitors (CNIs, *i.e.*, tacrolimus or cyclosporine) and steroids in the early post-transplant period. Tacrolimus (TAC) is the more frequently CNIs used in HIV recipients; Moreno *et al*[36] reported that the use of non-TAC based immunosuppression in HIV/HCV recipients was associated with an higher rates of severe OI. Several reports have demonstrated both the *in vitro*

Table 4 Comparison of human immunodeficiency virus+ *vs* human immunodeficiency virus- patients transplanted for hepatocellular carcinoma

Series	Pts number		Milan out		Alfa fetoprotein pre-LT		MiV+		HCC recurrence		Disease free survival (mo)	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Di Benedetto *et al*[48]	30	125	26.7%	43.2%	157.88 (1-2882)	327.64 (1-22455)	23.30%	16%	6.7%	14.4%	31.7 (1.28-68.78)	29.8 (0.43-75.79)
Viber *et al*[49]	16	58	31%	34%	16 (3-7154)	13 (1-552)	50%	43%	31%	15%	27 (14-79)	27 (2-78)

MiV+: Microvascular invasion present; HCC: Hepatocellular carcinoma; LT: Liver transplantation; HIV: Human immunodeficiency virus.

and *in vivo* effectiveness of rapamycin in reducing HIV replication[51,52], and Di Benedetto *et al*[53] found that rapamycin monotherapy was significantly beneficial in long-term immunosuppression maintenance and HIV control after LT. Mycophenolate mofetil is expected to be an effective immunosuppressive drug because of its efficacy in reducing HIV infection by both virological and immunological mechanisms[54,55]. Anti-lymphocyte depleting treatment with thymoglobulines (ATG) used as induction therapy at the moment of LT is usually not adopted in HIV recipients due to the development of severe lymphopenia. Moreover, several reports[14,34] reported an higher incidence of acute rejection after liver transplantation in HIV+ recipients; this fact has been related to the difficult management of post-transplant immuno-prophylaxis due to the major pharmacological interactions between CNIs and many antiretroviral drugs, both PI and NNRTI, causing instability in the blood concentration of CNIs through the cytochrome P3A4 (CYP3A4)-related metabolism. Most PI cause the overconcentration of CNIs by inhibiting CYP3A4, while most NNRTI cause decreased levels of CNIs by stimulating CYP3A4. However this problem might be overcome by the introduction of antiretrovirals that do not show interference with immunosuppressants *via* CYP450 (*i.e.*, enfuvirtide, raltegravir, maraviroc) as key drugs in the post-LT[56]. Also, a more widespread use of therapeutic drug monitoring (TDM) of both CNIs and antiretroviral drugs could be of help in targeting the appropriate trough levels reducing the risk of potential damaging drug to drug interaction in the early post-transplant period[57].

Treatment of HCV reactivation in HIV liver transplant recipients

Treatment of HCV recurrence in HIV-positive LT recipients represents a challenge for clinicians. Although better liver function should improve the tolerance to anti-HCV compounds after LT, other factors such as surgical complications, drug-to-drug interactions, and toxicity may complicate the management of HIV/HCV LT recipients. Data from the literature have shown how the HIV/HCV cohort is characterized by high treatment discontinuation rates due to drug toxicity and intolerance[58-60]. Factors such as priority of treatment, potential toxicities, concurrent C-ART options, and sustainability of current and future therapies should be taken into account when starting anti-HCV treatment in coinfected HIV/HCV recipients. Although attempts of early treatment (upon confirmation of histological recurrence) after LT have shown acceptable tolerability, low SVR rates were shown[61]. A liver biopsy to document the impact of HCV replication on the liver should always be performed, since the presence of high levels of HCV-RNA alone cannot be considered sufficient to determine the treatment start. In a study by Antonini *et al*[62], mortality due to HCV recurrence in HIV/HCV LT recipients reached rates up to 50%. Among patients with HCV reactivation, 30 out of 40 received post-LT anti-HCV dual therapy (timing, 10 ± 9 mo after LT) but only 17% displayed SVR, probably due to high early discontinuation rates (69%) and insufficient dosage of pegylated interferon and ribavirin (92%)[59]. In patients with genotype 1, recently approved HCV NS3/4A protease inhibitors have been demonstrated to enhance the efficacy of pegylated interferon and ribavirin. Limited but encouraging results have been reported in HIV/HCV LT recipients with HCV recurrence post-LT using triple therapy with boceprevir (BOC) or telaprevir (TVR). Compared to less than 40% SVR rates documented with dual therapy (pegylated interferon plus ribavirin), in naive HIV/HCV co-infected patients SVR was 61% and 74% in patients treated with BOC or TVR, respectively[63]. Safety and tolerability were comparable with those previously observed in HCV-monoinfected patients[63]. Besides known side effects (*i.e.*, anaemia, skin rash), major problems using the triple therapy are represented by the interactions between the immunosuppressive therapy and boosted anti-HIV PIs through the inhibition of CYP3A[64,65]. While PIs should be avoided with BOC, the use of atazanavir is possible in association with TVR, while higher TVR dosage is required using efavirenz-based C-ART regiments[66]. Furthermore, a very potent interaction with TVR has been described with immunosuppressive therapy that includes CYP3A and P-glycoprotein substrates such as cyclosporine or TAC[67]. Further studies on the HIV/HCV cohort using BOC or TVR are yet to be completed. There are also several new anti-HCV drugs under study with the potential for more tolerable effective future regimens[68]. Sofosvubir, a once-daily oral nucleotide analogue inhibitor still under investigation may be available in the next future for interferon-free regimens in genotype 2 and 3 and in combination with ribavirin and pegylated interferon for other genotypes. Preliminary data showed a median decline of HCV-RNA viral load of more than 4 log after one week of treat-

ment in a group of 30 HIV/HCV coinfected patients on stable C-ART therapy and preserved CD4 T cell count [52nd Interscience Conference on Antimicrobials and Chemotherapy, oral communication]. Sofosvubir (in association with pegylated interferon and/or ribavirin), has been provided for compassionate use in HIV/HCV patients undergoing LT with severe HCV reinfection and life expectancy below 6 mo.

Post-liver transplant infections and malignancies in HIV/HCV coinfected patients

Despite the use of antimicrobial prophylaxis and infection control measures, infections still represent a major cause of mortality after LT[69]. It is estimated that up to 80% of LT recipients will develop at least one infection during the first year post-LT[70]. Furthermore, during the first 3 years after LT death may occur due to OI[69]. In this scenario, HIV/HCV LT recipients may be particularly susceptible to infections due to their intrinsic CD4/CD8 dysfunction and to pharmacological immunosuppression that may interfere with an effective C-ART; nevertheless, the literature has demonstrated that bacterial and fungal infection rates in the HIV/HCV cohort are not dramatically different from non-HIV-infected LT recipients. A Spanish study on 84 HIV/HCV patients undergoing LT showed that 58 (69%) of them had at least one documented post-LT infection. Of these, nearly a half where classified as severe infections[14]. Occurrence of invasive fungal infections (n = 6, two cases of zigomycosis, two esophageal candidiasis, one aspergillosis, one pneumocystis jiroveci pneumonia) were documented in 7% of patients and correlated with high rates of mortality (P = 0.008). Among other infections, two CMV reactivations and two cases of pulmonary tuberculosis occurred. In a German study on 32 HIV-positive LT recipients, 7 (22%) died of sepsis[71]; CMV viremia was detected in 5 (16%) and one Kaposi sarcoma was documented 4.5 mo post-LT. No deaths due to HIV-related infections or malignancies were recorded in a large US multicentric study encompassing 89 patients[35]. Nevertheless, in the same study, patients or graft loss due to sepsis or multi-organ failure was more frequent in the HCV/HIV group compared to HCV monoinfected LT recipients (32% *vs* 15%, respectively)[35]. Overall, low rates of malignancies have been reported in HIV-positive patients undergoing liver and kidney transplantation[72].

CONCLUSION

The chronicity of HIV disease and the consequent increase of ESLD along with C-ART-related complications will likely increase the request for LT in the HIV cohort. The challenges associated with the care of these patients require a joint effort by a multidisciplinary team with expertise in managing surgical complications, immunosuppressants and C-ART regimens. A close patients follow up is a crucial factor in achieving positive results in HIV-positive patients undergoing LT. At present, liver transplantation for ESLD with an etiology different from HCV in HIV-infected patients should be considered not different and with the same prioritization compared to non-HIV population. For ESLD due to HIV/HCV coinfection, the long-term results are reported to be worst than HCV monoinfected, especially when transplantation is performed at the same MELD score than HCV counterparts. Moreover mortality in the waiting list is higher at the same MELD. Therefore, careful follow-up before entering the waiting list and during time on waiting list should be provided to HIV/HCV coinfected patients especially after episodes of liver decompensation. Also, pursuing alternative source of donors, such as HIV or HCV infected donors or donors with unknown infective risks could be a potential source allocable to coinfected HIV/HCV recipients. Management of surgical complications, infections, and drug-to-drug interferences is possible in the post-transplant for coinfected HIV/HCV LT recipients. HCV recurrence currently represents the major challenge in this cohort; nevertheless, new options for the treatment of HCV infection in coinfected HIV/HCV LT patients may be available in the near future.

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