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HIV-positive to HIV-positive liver transplantation: To be continued

To the Editor:

Although the recently reported outcomes of human immunodeficiency virus (HIV)-positive to HIV-positive liver transplantation (LT) performed in the UK and Switzerland are certainly promising, several challenges remain before this transplant option can be expanded.[1,2]

The main risks of this procedure include: HIV superinfection, transmission of drug resistance and/or donor-related infections, drug-related liver dysfunction, and an increased risk of rejection.

For the first time in Italy, an HIV-positive man received successful LT for multifocal hepatocellular carcinoma (HCC) on a background of viral cirrhosis from an HIV-positive brain-dead donor in May 2017. The 50-year-old recipient with a 32-year history of infection secondary to injection drug use had refused to take antiretroviral therapy (ART) for almost 20 years of asymptomatic infection. After esophageal candidosis (CDC stage C3) in 2005, a regimen with efavirenz plus tenofovir/emtricitabine was started with clinical and immunological improvement. ART was switched in 2015 to rilpivirine and in July 2016 to dolutegravir, maintaining tenofovir/emtricitabine. Due to the long duration of infection and persistently undetectable HIV-RNA in the previous decade, HIV genotypic resistance testing did not show significant resistance to any drug class before LT. He was negative for HLAB*5701, while the virus strain was CCR5 tropic.

Advanced liver disease was secondary to hepatitis B virus, hepatitis delta virus co-infection and previous hepatitis C virus infection. In 2016, five years after successful locoregional treatment of the HCC, two new untreatable nodules (within Milan criteria) were diagnosed and the patient was admitted to the waiting list for LT. The patient's clinical history, and management of HIV infection over time are reported in the table with details of the other two HIV-to-HIV LT reported in the literature (see Table 1).

The donor was a 52-year-old HIV-positive man who died from stroke. He was under his first ART regimen (abacavir/lamivudine and dolutegravir) with no history of treatment failure. At the time of organ donation his CD4 cell count was 501 cells/mm^3 (23%) and plasma HIV-RNA was detectable, with 198 copies/ml, probably resulting from ART suspension due to his severe clinical condition. HIV genotypic resistance test was available four days after liver procurement and no resistance-associated mutations were reported for nucleosidic and non-nucleosidic reverse transcriptase inhibitors, protease inhibitors or integrase inhibitors.

The graft rapidly recovered function after transplant, and no surgical or medical complication occurred. HIV-positive transplant recipients are known to have a higher rejection rate than negative subjects.[3,4] The recipient received an immunosuppressive regimen associating basiliximab induction, low-dose steroids and tacrolimus. ART with the previous regimen of tenofovir/emtricitabine and dolutegravir was resumed on post-transplant day 3. The patient was discharged on postoperative day 16 and liver function tests were in the normal range three weeks after LT. HIV-RNA remained undetectable from the second day after LT. The virus maintained CCR5 tropism and HBV-CMV-EBV-HHV6 and HVV8 viremia were always negative after transplant. No rejection episodes or infections occurred up to one year after LT.

Recipient and donor selection are still evolving in this uncommon transplant process. During donor assessment, previous ART regimens, HIV genotypic resistance tests and previous or ongoing opportunistic infections must be evaluated, and the risk of superinfection with a resistant HIV strain must be addressed. HIV genotypic resistance as a prognostic factor for post-transplant outcomes is not yet known. Superinfection with an HIV strain resistant to one or more antiretrovirals could decrease the HIV treatment options. This issue would be especially relevant in transplanted patients for whom ART might be limited by interactions between antiretrovirals and immunosuppressive drugs. In the case presented, both donor and recipient had been HIV-infected for a long time, but they had experienced few ART regimens with no history of virological failure. While the recipient's medical history was fully known and the patient was on stable ART with undetectable HIV-RNA, the donor was on ART but had a low-level viremia in the days before organ donation, possibly secondary to sub-optimal adherence and absorption during the acute neurological event. In this setting, the availability of his medical history of therapeutic adherence and undetectable HIV-RNA in the previous months reduced the chance of resistance-associated mutations as a possible cause of low-level viremia and made organ donation a safe procedure even in this setting. The similar successful anti-HIV regimens in both donor and recipient allowed the same ART to be continued after LT, with persistent virological control and no side-effects.

Interestingly, donor liver biopsies showed only mild steatosis, strengthening the good status of the organ even in the setting of long-lasting HIV infection and continuous exposure to ART with potential hepatotoxicity.

Following two LTs from HIV-positive donors performed elsewhere in the world,[1,2] we reported the first successful HIV-to-HIV LT in Italy with more than one year of follow-up. We are optimistic that these preliminary experiences will encourage the adoption of this practice and its reporting, considering every HIV-positive individual a potential organ donor and thereby optimizing the donor pool, as recently reported in the US.[5] Ongoing updates to HIV-to-HIV LTs are mandatory, and physicians involved in the care of HIV-positive patients should clearly and swiftly report data on recipient outcomes to better understand the concerns related to this uncommon transplant setting.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Keywords: Human immunodeficiency virus; Liver donation; Liver transplantation.

Table 1. Literature reported cases. Patient's clinical history, and management of HIV infection over time.

Author Country Year	Recipient age/sex; HIV diagnosis; cause of infection; liver disease coinfection	Recipient ART regimens (drug/from)	CD4 cell count HIV viral load	Donor age/sex; cause of death; HIV diagnosis; coinfection; CD4 cell count; HIV viral load; ongoing ART	Immunosuppression	Viral load after LT	Follow-up
Calmy, A Switzerland 2016	53-year-old man; HIV from 1987; drug abuse; viral cirrhosis; HCV, HBV, HDV	ZDV + zalcitabine/1992 IDV + stavudine + lamivudine/1997 ART interruption/ 2001–2002 ABC + EVF + ddl/2002 RPV + TDF + FTC/2013 RPV + TDF + FTC + DTG/ after LT	300–400 cells/mm^3 HIV RNA <50 copies/ml	75-year-old man; cerebellar hemorrhage; HIV from 1989; 298 cells/mm^3 (21%); HIV RNA <40 copies/ml; TDF + FTC + DTG	Tac, MMF	Undetectable	5 months
Hathorn, E U.K. 2016	47-year-old man; HIV; N/A; HCC; Hemophilia A; HCV	ART started/1998 FTC-TDF + EVF/2004	N/A HIV RNA <20 copies/ml	N/A; N/A; HCV positive (RNA−); HIV viremia positive; ART not known	Tac, MMF	Positive, resuppression 7 weeks after LT	5 years
Present case Italy 2018	50-year-old man; HIV from 1995; drug abuse; HCC; HCV, HBV, HDV	EFV + TDF-FTC/2005 RPV + TDF-FTC/2015 DTG + TDF-FTC/2016 DTG + TDF-FTC/after LT	420 cells/mm^3 HIV RNA <20 copies/ml	52-years-old man; stroke; HIV from 1998; 501 cells/mm^3 (23%); HIV RNA 198 copies/ml; ABC + lamivudine + DTG	Basiliximab induction, Tac, steroids (low-dose, discontinued)	Undetectable	1 year

ABC, abacavir; ART, antiretroviral therapy; ddl, didanosine; DTG, dolutegavir; EFV, efavirenz; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis d virus; HIV, human immunodeficiency virus; IDV, indinavir; LT, liver transplant; MMF, mycophenolate mofetil; N/A, not available; RPV, rilpivirine; TDF, tenofovir; Tac, tacrolimus; ZDV, zidovudine.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.06.026.

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Author names in bold designate shared co-first authorship

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