HIV-Positive-to-HIV-Positive Liver Transplantation

CALMY, Alexandra, et al.

Abstract

Most countries exclude human immunodeficiency virus (HIV)-positive patients from organ donation because of concerns regarding donor-derived HIV transmission. The Swiss Federal Act on Transplantation has allowed organ transplantation between HIV-positive donors and recipients since 2007. We report the successful liver transplantation from an HIV-positive donor to an HIV-positive recipient. Both donor and recipient had been treated for many years with antiretroviral therapy and harbored multidrug-resistant viruses. Five months after transplantation, HIV viremia remains undetectable. This observation supports the inclusion of appropriate HIV-positive donors for transplants specifically allocated to HIV-positive recipients.

Reference


PMID: 27109874
DOI: 10.1111/ajt.13824
Case Report

HIV-Positive-to-HIV-Positive Liver Transplantation

A. Calmy1,*1, C. van Delden2†, E. Giostra3, C. Junet4, L. Rubbia Brandt5, S. Yerly6, J.-P. Chave7, C. Samer8, L. Elkrief3, J. Vionnet9 and T. Berney3 on behalf of the Swiss HIV and Swiss Transplant Cohort Studies

1HIV Unit, Geneva University Hospitals, Geneva, Switzerland
2Transplant Infectious Diseases Unit, Geneva University Hospitals, Geneva, Switzerland
3Division of Transplantation, Geneva University Hospitals, Geneva, Switzerland
4Private Practice, Geneva, Switzerland
5Division of Pathology, Geneva University Hospitals, Geneva, Switzerland
6Virology Laboratory, Geneva University Hospitals, Geneva, Switzerland
7Private Practice, Lausanne, Switzerland
8Division of Clinical Pharmacology and Toxicology, Geneva University Hospitals, Geneva, Switzerland
9Division of Gastroenterology and Division of Transplantation, CHUV, Lausanne, Switzerland
*Corresponding author: Alexandra Calmy, alexandra.calmy@hcuge.ch
†Both authors contributed equally to the manuscript.

Most countries exclude human immunodeficiency virus (HIV)-positive patients from organ donation because of concerns regarding donor-derived HIV transmission. The Swiss Federal Act on Transplantation has allowed organ transplantation between HIV-positive donors and recipients since 2007. We report the successful liver transplantation from an HIV-positive donor to an HIV-positive recipient. Both donor and recipient had been treated for many years with antiretroviral therapy and harbored multidrug-resistant viruses. Five months after transplantation, HIV viremia remains undetectable. This observation supports the inclusion of appropriate HIV-positive donors for transplants specifically allocated to HIV-positive recipients.

Abbreviations: ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HBIG, hepatitis B immunoglobulins; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; HOPE, HIV Organ Policy Equity; LT, liver transplant; MELD, Models for End-Stage Liver Disease; RT, reverse transcriptase; SHCS, Swiss HIV Cohort Study

Received 01 April 2016, revised 08 April 2016 and accepted for publication 09 April 2016

Introduction

Concerns about donor-derived human immunodeficiency virus (HIV) transmission have excluded HIV-positive patients from organ donation lists in most countries. This leads to the loss of an estimated 356 potential organ donors per year in the United States (1). HIV-positive solid organ transplant candidates remain disadvantaged on waiting lists with an increased risk of death, particularly in HIV-hepatitis C virus (HCV)–coinfected individuals with liver disease (2–4). Despite a higher relative risk of experiencing graft failure compared to HIV-negative controls, HIV status was not associated with an increased risk of death in a cohort of solid organ transplant recipients in the United States (5). The concern that transplantation of organs from HIV-positive donors might harm transplant recipients remains. Indeed, transmission of a new HIV strain to an immunosuppressed HIV-positive recipient could potentially lead to uncontrolled viral replication, immune dysregulation, and opportunistic infections (4,6). So far, reports on the transplant of HIV-positive organs have been limited to kidney transplantation in South Africa from treatment-naive or first-line antiretroviral therapy (ART)–treated HIV-positive donors to HIV-positive recipients (7). The Swiss Federal Act on Transplantation and its bylaws has allowed transplantation from HIV-positive donors to HIV-positive recipients since July 2007 (Data S1, Document 1) (8,9). Similarly, the HIV Organ Policy Equity (HOPE) act passed by the United States Congress in November 2013 legalized such transplants, but only in the setting of an approved research protocol (10). From 2008 to 2014, 569 HIV-positive individuals died in Switzerland, with liver-related deaths accounting for nearly 14% of all reported deaths (11). During this period of time, 14 HIV-positive individuals benefited from a liver transplant (LT) from HIV-negative donors (Franziska Schön-Affolter, personal communication). We report the first documented case of successful LT between an ART-experienced HIV-positive donor and recipient.

Case Report

The recipient

A 53-year-old HIV-positive man was offered a liver from a brain death deceased HIV-positive donor in October 2015 in Switzerland. He was diagnosed HIV-positive secondary to intravenous drug abuse in 1987 with a Centers for Disease Control and Prevention (CDC) stage B3
(herpes zoster) and a CD4 cell count nadir 78 cells/mm³. Initial treatment consisted of zidovudine and zalcitabine in 1992, followed in 1997 by a combination of indinavir, stavudine, and lamivudine until a virological escape and a M184V mutation were identified in 2001. Following a short period of structured treatment interruption between 2001 and 2002, he resumed an ART of abacavir, efavirenz, and didanosine (switched in 2003 to tenofovir) late in 2002. Since 2003, HIV-RNA levels have remained below the threshold of detectability (50 copies/mL) with a stable CD4 cell count between 300 and 400 cells/mm³. In 2013, a combination of rilpivirine, tenofovir, and emtricitabine was initiated (Figure 1). Chronic hepatitis C virus (HCV) genotype 4 coinfection was diagnosed in 1997 with a positive HCV RNA viremia that became undetectable in 2004 without specific therapy. Hepatitis B virus (HBV) serological status was hepatitis B surface antigen positive, antibodies to the hepatitis B core antigen positive, with undetectable HBV DNA viremia under tenofovir therapy. Seroconversion from hepatitis B envelope antigen (HBsAg) to anti-HBe occurred in 2010. A replicative hepatitis D virus (HDV) infection (7.3 E+8 copies/mL) with sustained hepatic cytolysis occurred in 2011. Pegylated interferon was initiated but stopped after four doses because of adverse drug reactions. At the time of pretransplant evaluation, the Child-Pugh score was B7 and the Model for End-Stage Liver Disease (MELD) score was 9. The patient was registered on the waiting list in November 2014. Clinical condition and liver function tests rapidly declined thereafter, with poorly controlled ascites and recurring episodes of encephalopathy. In June 2015, the Child-Pugh score had increased to C10, but the MELD score remained low (11). Given this particular situation, he was granted a nonstandard MELD exception for incapacitating encephalopathy and refractory ascites. Both a liver biopsy and explant examination

Figure 1: Clinical timeline of the HIV-positive liver transplant recipient. Shown are key dates from 1987 throughout January 2016 (5 months after LT) regarding the human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis D virus (HDV), and hepatitis C virus (HCV) infections, in terms of diagnosis and therapies. HIV, human immunodeficiency virus; LT, liver transplant; MMF, mycophenolate mofetil; AntiHBs, antibodies to the hepatitis B surface antigen.
confirmed the diagnosis of cirrhosis on HBV/HDV-related chronic hepatitis of moderate inflammatory activity (Data S1, Document 2A–C).

**The donor**

The donor was a 75-year-old man who died of a cerebellar hemorrhage. He was diagnosed HIV-positive in 1989 (transmission route—bisexual contacts; CDC stage C3 [cryptosporidiosis, esophageal candidiasis, herpes zoster]). His ART consisted initially of zidovudine, lamivudine, and indinavir started in the setting of detected multiple resistance mutations in 1996. Due to a virological failure and the presence of mutations associated with drug resistance in 2002 (Figure 2), his drug regimen was modified to nevirapine, boosted lopinavir, and abacavir. Thereafter, his HIV-RNA viremia remained below the detection limit with a stable CD4 cell count around 400 cells/mm³. In 2011, he was started on raltegravir, modified for dolutegravir 15 days prior to his death, in conjunction with tenofovir and emtricitabine. Following information by his primary care physician that Swiss law allowed him to donate his organs to HIV-positive recipients, he provided written explicit consent for organ donation in September 2015 (Data S1, Document 3). At the time of donation his laboratory values (including white blood cell count, liver and kidney function tests) were normal; CD4 cell count was 298 cells/mm³ (21%) and HIV-RNA below the detection level of 40 copies/mL.

### Resistance testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutations list</th>
<th>Interpretation</th>
<th>Mutations list</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine/Emtricitabine</td>
<td>41L, 210W, 215Y</td>
<td>S</td>
<td>184Y</td>
<td>R</td>
</tr>
<tr>
<td>Didanosine</td>
<td>41L, 215Y</td>
<td>R</td>
<td>41L, 215Y</td>
<td>R</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutations list</th>
<th>Interpretation</th>
<th>Mutations list</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td></td>
<td>S</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Etravirine</td>
<td></td>
<td>S</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>S</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td></td>
<td>S</td>
<td></td>
<td>S</td>
</tr>
</tbody>
</table>

### Protease inhibitors (PI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutations list</th>
<th>Interpretation</th>
<th>Mutations list</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/r</td>
<td>361</td>
<td>S</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>63P</td>
<td>S</td>
<td>63P</td>
<td>S</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>63P</td>
<td>S</td>
<td>361</td>
<td>S</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td></td>
<td>S</td>
<td>361</td>
<td>S</td>
</tr>
<tr>
<td>Saquinavir/r</td>
<td></td>
<td>S</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Tipranavir/r</td>
<td></td>
<td>S</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td></td>
<td>S</td>
<td>361</td>
<td>S</td>
</tr>
</tbody>
</table>

* S, susceptible
* R, resistant
* ?, possible resistant

**Figure 2:** Genotypic HIV resistance of the HIV-positive liver donor. Shown are genotypic resistance obtained through population-based sequencing of the full protease gene and codons 28–225 of the reverse transcriptase gene interpreted according to the ANRS algorithm 2015 version 25 (http://hivfrenchresistance.org/) (22). No further determinations of HIV resistance were performed due to continuous viral suppression. HIV, human immunodeficiency virus; ANRS, Agence Nationale de Recherche sur le Sida et les hépatites.
Liver transplantation

A transplant infectious diseases physician informed the recipient candidate about potential virus transmission and the requirements to adapt his anti-HIV therapy due to different viral resistances. The patient accepted the risk and signed an informed consent for liver transplantation (Data S1, Document 4). No ethical clearance was necessary due to the permissive law in Switzerland. A donor per-operative liver biopsy identified a macrovesicular steatosis of minimal extent (less than 10%) on frozen section histology and mild portal inflammation, not contraindicating the organ donation (Data S1, Document 2D). We were unable to detect HIV-RNA by polymerase chain reaction performed on cells extracted from formalin-fixed paraffin-embedded donor liver tissue despite adequate tissue conservation. Posttransplant, the liver graft showed immediate function, and no surgical or medical complications occurred. The transplant serostatus was the following: cytomegalovirus D+/R− (positive donor, negative recipient), toxoplasmosis D+/R+, Epstein-Barr virus D+/R+. He received a standard, steroid-free immunosuppressive regimen associating basiliximab induction, as well as tacrolimus and mycophenolate mofetil. To prevent HBV recurrence, hepatitis B immunoglobulins (HBIG) were infused during the transplant surgery.

Posttransplant care

Rilpivirine/tenofovir/emtricitabine were restarted on Day 2 posttransplant, together with raltegravir and subcutaneous enfuvirtide to cover for the donor’s HIV resistance genotypes. The patient was discharged on posttransplant Day 22 receiving prophylactic valgancyclovir and trimethoprim and sulfamethoxazole in addition to his immunosuppression and ART. ART was modified 3 months after transplantation to a fixed-dose combination of rilpivirine/tenofovir/emtricitabine and dolutegravir. Rilpivirine plasma levels, measured at 6 days and 8 weeks after transplantation, were in the normal to lower therapeutic range (25th to 40th percentile) and decreased at weeks 15 and 18 posttransplant to the 10th lower percentile (30 ng/mL). Plasma levels of dolutegravir were lower than expected after a dose of 50 mg twice a day at weeks 15 and 18. Tacrolimus dosage was easily adjusted to maintain trough levels in the desired range (8–15 ng/mL). HBV and HDV DNA, as well as HIV and HCV RNA, remained undetectable after transplantation (Figure 1). No rejection episode occurred during the 5-month follow-up period.

Discussion

We report the first successful liver transplantation, to our knowledge, from an HIV-positive donor to an HIV-positive recipient. So far, report of transplantation of organs from HIV-positive donors has been restricted to the description of the outcome in 27 HIV-positive recipients who received kidneys from HIV-positive donors in South Africa (7). Five years posttransplantation, both cumulative patient and graft survival (74% and 84% with censoring for death with function, respectively) were similar to those in HIV-positive recipients of an HIV-negative organ. In this study, however, both donors and recipients were highly selected. To reduce the risk of resistant-virus transmission, donors were either ART-naive or had taken only first-line ART, while CD4 T cell counts of at least 200/mm³ and undetectable plasma HIV RNA levels were prerequisites in potential recipients taking ART for at least 3 months. In addition there has been a recent report (March 2016) in the news media of a liver and a kidney transplant performed in Baltimore from an HIV+ donor to HIV+ recipients.

The present report is original in many ways. Both donor and recipient had been seropositive for roughly 30 years, had been treated with several ART regimens, and had negative viral assays for HIV at the time of transplantation. Both harbored HIV strains with resistance mutations on the reverse transcriptase (RT) gene, which were non-identical. Thus, to decrease the risk that the transplanted liver would transmit a viral strain with distinct mutations, we adapted the recipient’s pretransplant suppressive ART to the donor’s HIV genotype by adding an integrase inhibitor and a short course of enfuvirtide. This strategy has thus far proven successful; at 5 months, HIV viremia remains suppressed below the threshold of detection of 20 copies/mL. At this point, there is no indication that immunosuppressive therapy has enabled an increase in HIV pathogenicity and thus potentiated its spread, as previously feared (6).

Outcome in HIV/HBV-coinfected LT recipients is excellent, and comparable to that of HBV-monoinfected patients receiving combined HBIG and HBV antiviral therapy (12,13). Accordingly, our patient received HBIG with tenofovir, and HBV viremia remained undetectable. In contrast, HIV–HCV coinfection is of concern in LT, with increased risks of rejection and reduced graft and patient survival, particularly when donors are 50 years of age or older (14,15). In the present case, the recipient was coinfected with HBV, HCV, and HDV, while the donor was 75 years old. However, the risk of a poor outcome was likely mitigated by the recipient’s spontaneous clearance of HCV viremia before LT and low MELD score. Indeed, the pre-LT MELD score was identified as the only predictor of survival in a French multicenter cohort of HIV–HCV coinfected LT recipients (16). This has led experts to advocate the use of HIV-positive organs to facilitate access to transplantation for those with lower MELD scores (16,17). Furthermore, an eventual HCV infection recurrence in our recipient would very likely be controlled with the newly available highly active anti-HCV agents. Despite long-standing exposure to multiple antiviral drugs, the histology of the transplanted liver revealed only minor macrovesicular steatosis. Furthermore, hepatic function recovered rapidly after LT, lessening the fear that the transplant might have suffered from drug-
induced damage. Longer follow-up is certainly needed to ensure both the virologic and functional safety of this procedure.

Drug–drug interactions remain potentially challenging in HIV transplant recipients (18). Dolutegravir, rilpivirine, and tacrolimus are substrates of cytochrome P450 (CYP) 3A (19, 20). Dolutegravir plasma levels were lower than expected in the recipient, and rilpivirine and tacrolimus plasma concentrations gradually decreased to the desired therapeutic range. No CYP3A inducer was included among the recipient’s medications that could explain the increased drug clearance and reduced plasma concentrations of CYP3A substrates. Donor genetic variability could account for the phenotypic alterations observed in the recipient (21).

The immunologic and virologic control produced by effective ART in both donor and recipient was essential to the success of this LT. With currently available antiretrovirals, HIV-RNA can be rapidly suppressed in the vast majority of cases and should not be a major concern in the decision to proceed with transplantation.

Another issue could be the need to decide on the safety of organ transplantation in the absence of adequate documentation of the clinical history of both HIV+ donor and recipient. This includes viral rebound episodes and genotypic resistance, as well as potential active opportunistic infections and/or concurrent oncologic diseases. This may in certain situations impose limits to organ donation. In Switzerland over 75% of all HIV+ patients, including both our donor and recipient, are included in the Swiss HIV Cohort Study (SHCS), allowing precise documentation of all HIV-related events (22). Moreover in 2016, with the advent of potent ARTs, the vast majority of HIV strains can be successfully treated. In certain circumstances such as the absence of ART, HIV+ patients with active HIV viral replication may be considered as potential donors.

The Swiss Federal Act on the Transplantation of Organs, Tissues and Cells (810.21) went into effect on July 1, 2007 (8). Bylaw 810.211 (article 6.2.1) authorizes the transplantation of organs from HIV-positive donors to HIV-positive recipients (9). The HOPE Act signed into law on July 1, 2007 (810.21) went into effect on July 1, 2016; 16: 2473–2478. Effective ART has revolutionized the health of HIV-positive individuals. Treating physicians of HIV-infected individuals should inform their patients if the option exists for organ donation, and encourage policymakers to consider lifting restrictions on organ donation from HIV-positive individuals for HIV-positive recipients.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Acknowledgments


References


Supporting Information

Additional Supporting Information may be found in the online version of this article.

Data S1: Document 1 refers to the original French text of the Swiss Transplantation bylaw 810.211. Document 2 shows the recipient and donor liver images. Document 3 is the original organ donation consent. Document 4 is the original recipient transplant consent.