

First Canadian Case Report of Kidney Transplantation From an HIV-Positive Donor to an HIV-Positive Recipient

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Abstract

Rationale: Kidney transplantation has become standard of care for carefully selected patients living with human immunodeficiency virus (HIV) and end-stage renal disease (ESRD) in the highly active antiretroviral therapy (HAART) era. American and European prospective cohort studies have reported similar patient and graft survival compared with HIV-negative kidney transplant recipients. Despite an increased rate of acute rejection, partially due to drug interactions, HIV immunovirologic parameter generally remains under control during immunosuppression. A few cases of kidney transplantation between HIV-infected patients were done in South Africa and showed favorable results. No cases of kidney transplantation from an HIV-positive donor in Canada have previously been reported.

Presenting concerns of the patient: A 60-year-old Canadian man with HIV infection presented in 2007 with symptoms compatible with acute renal failure secondary to IgA nephropathy. Chronic kidney disease resulted after the acute episode.

Diagnoses: Hemodialysis was started in 2012. The patient was referred for a kidney transplantation evaluation.

Interventions: The patient underwent kidney transplantation from an HIV-positive donor in January 2016. The recipient's antiretroviral regimen consisted of abacavir, lamivudine, and dolutegravir. No drug interactions have been reported between these antiretrovirals and the maintenance immunosuppressive regimen used.

Outcomes: The outcome at 7 months post transplantation was excellent, with good graft function and adequate control of HIV replication, in the absence of opportunistic infections at a time when immunosuppression is at its highest intensity. No acute rejection was reported. An episode of bacteremic graft pyelonephritis due to *Enterococcus faecalis* was successfully treated after transplantation.

Novel finding: With careful selection of patient, kidney transplantation between HIV-infected patients is a viable option. The use of antiretroviral drugs free of interactions simplified the dosing and management of the immunosuppressive drugs.

Abrégé

Raisonnement: La transplantation rénale fait désormais partie des soins prodigués spécifiquement aux patients porteurs du VIH (virus de l'immunodéficience humaine) et présentant une insuffisance rénale terminale (IRT) à l'ère de la thérapie antirétrovirale. Des études de cohorte prospectives américaines et européennes ont rapporté une survie semblable du greffon et du receveur de la greffe chez ces patients, lorsque comparés aux receveurs d'une greffe non porteurs du VIH. En dépit d'un taux plus élevé de rejet aigu, attribuable en partie aux interactions médicamenteuses, les paramètres immunovirologiques du VIH sont demeurés stables sous traitement par les immunosuppresseurs. Quelques cas de transplantations rénales entre patients séropositifs ont été effectués en Afrique du Sud et ont montré des résultats favorables. À ce jour, on ne rapportait aucun cas de transplantation rénale provenant d'un donneur porteur du VIH au Canada.

Présentation du cas d'un patient: En 2007, un Canadien de 60 ans porteur du VIH s'est présenté avec des symptômes compatibles à l'insuffisance rénale aiguë secondaire à une néphropathie à IgA. Cet épisode aigu a par la suite évolué vers l'insuffisance rénale chronique.

Diagnostic: L'insuffisance rénale terminale a été diagnostiquée en 2012. Dès lors, un traitement par hémodialyse a été initié et le patient a été recommandé pour une évaluation en vue d'une transplantation.

Interventions: Le patient a subi une greffe avec un rein provenant d'un donneur séropositif en janvier 2016. Le traitement antirétroviral du receveur était constitué d'abacavir, de lamivudine et de dolutegravir. Aucune interaction médicamenteuse n'a été rapportée entre ces antirétroviraux et le traitement immunosuppresseur de maintien administré.



Résultats: En plus d'une bonne reprise de la fonction du greffon et du contrôle adéquat de la réplication du VIH, on a constaté la réussite de l'intervention lors du suivi du patient effectué 7 mois après la transplantation par l'absence d'infections opportunistes à un moment où l'immunosuppression est à son maximum. Aucun rejet aigu n'a été rapporté par contre, un épisode de pyélonéphrite bactérienne du greffon, attribuable à *Enterococcus faecalis*, est survenu à la suite de la transplantation, mais l'infection a été traitée avec succès.

Observations nouvelles: On a constaté que la sélection rigoureuse des patients rendait possible la transplantation rénale entre patients porteurs du VIH. De plus, l'utilisation d'antirétroviraux qui ne causent aucune interaction médicamenteuse a simplifié l'ajustement de la posologie des immunosuppresseurs administrés.

Cas discuté: Nous rapportons le cas d'un Canadien de 60 ans porteur du VIH et ayant subi une greffe de rein provenant d'un donneur lui aussi séropositif. Le traitement antirétroviral du receveur était composé d'abacavir, de lamivudine et de dolutégravir. Aucune interaction médicamenteuse n'a été rapportée entre les antirétroviraux et le traitement immunosuppresseur de maintien. Sept mois après l'intervention, le patient se portait bien, comme en fait foi un taux de créatinine sérique de 155 µmol/L mesuré lors de la plus récente visite de suivi. La charge virale du patient (quantité d'ARN du VIH dans le sang) s'est avérée indétectable et le compte des lymphocytes T CD4 est demeuré au-dessus de 300 cellules/µl pendant toute la période de suivi. Le patient n'a présenté aucun signe indiquant la présence d'une maladie associée au SIDA, ni d'un rejet aigu du greffon. Enfin, un épisode de pyélonéphrite bactérienne du greffon, attribuable à *Enterococcus faecalis*, est survenu après la transplantation, mais l'infection a été traitée avec succès.

Conclusions: Nous rapportons la première transplantation de rein réalisée au Canada entre un donneur séropositif et un receveur, lui aussi porteur du VIH. L'évolution du patient après l'intervention s'est avérée excellente, on a constaté une bonne reprise de la fonction du greffon et un contrôle adéquat de la réplication du VIH, une réussite confirmée par l'absence d'infections opportunistes à un moment où l'immunosuppression est à son maximum. De plus, l'utilisation d'antirétroviraux qui ne causent aucune interaction médicamenteuse a simplifié l'ajustement de la posologie des immunosuppresseurs administrés.

Découverte: La sélection rigoureuse des patients rend possible la transplantation rénale entre patients séropositifs atteints d'IRT et donneurs eux aussi porteurs du VIH.

Keywords

kidney transplantation, HIV, HIV-positive donor, HIV-positive recipient

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What was known before

Worldwide experience in solid organ transplantation from HIV-infected donor is limited to case series.

What this adds

We describe the first Canadian HIV-positive to HIV-positive kidney transplant. We recommend that this practice continue on a case-by-case basis, with continued reporting of outcomes. If safe, kidney transplantation from HIV-positive donors could increase access for HIV-positive patients with ESRD.

Introduction

Highly active antiretroviral therapy (HAART) has drastically improved the survival of human immunodeficiency virus (HIV)-infected individuals. Consequently, chronic conditions such as end-stage renal disease (ESRD) have become an important issue in HIV treatment. Numerous studies have shown favorable outcomes of kidney transplantation for HIV-infected patients, with patient and graft survival in HIV-positive recipients that are similar to those observed in HIV-negative patients.¹⁻³ No progression of HIV was observed in the presence of immunosuppression, and viral loads remained

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undetectable. Drug interactions between antiretrovirals and immunosuppressive agents are probably responsible for the increased rates of acute rejection that have been described previously.¹ This has led the International Antiviral Society to recommend with strong support, in its latest publication, that every HIV-infected patient with ESRD should be evaluated for kidney transplantation.⁴

Although kidney transplantation is now a viable option for HIV-infected patients with ESRD, studies have reported that they are less likely to be put on a kidney transplant waiting list than their non-HIV-infected counterparts. In a retrospective cohort study, only 20% of 309 potentially eligible HIV-infected patients evaluated for kidney transplantation were wait-listed compared with 73% of HIV-negative patients evaluated over the same period. CD4 T-cell count <200 cells/ μ L at the initial evaluation, black race, and history of drug use were associated with failure to complete the evaluation.⁵

This disparity in terms of access to the kidney transplant waiting list is concerning, especially given that HIV-infected individuals have lower survival on dialysis compared with non-infected patients.⁶ In Canada, close to 3500 patients are waiting for a kidney transplant, with a median waiting time of 3.5 years.⁷ Given the ongoing organ shortage, novel approaches to maximize the use of organs for transplantation is crucial. Kidney transplantations from HIV-positive donors to HIV-positive recipients were performed in South Africa with favorable results. Although legislative changes in the United States have defined eligibility criteria for HIV-infected organ donation, data on the viability of HIV-positive donor to HIV-positive recipient kidney transplantation remain scarce.^{8,9} One of the main concerns with this type of transplantation is the transmission and replication of a strain with a different resistance profile in the recipient if the post-transplant antiretroviral therapy does not take into account the profile of the donor's and the recipient's strain. Nevertheless, this situation is less likely to occur if adequate virological suppression is achieved concomitantly in the donor and the recipient.

Presenting Concerns

A 60-year-old man who has sex with men was diagnosed with HIV in 2001 (Table 1). At the time of presentation, the plasma RNA HIV viral load was 29 079 copies/mL. The nadir CD4 T-cell count was 190 cells/ μ L. No baseline genotyping was done at the time. He was started on HAART in 2002. The patient suffered from chronic intestinal parasitosis with *Entamoeba coli* and *Blastocystis hominis*, which was completely treated in 2004. The patient never developed an AIDS-defining illness. In 2007, he developed chronic kidney disease (CKD) due to IgA nephropathy. His antiretroviral therapy at that time was abacavir, lamivudine, and efavirenz. His CKD progressed to ESRD over the following 5 years,

Table 1. Timeline.

2001	Diagnosis of HIV
2002	Initiation of antiretroviral therapy
2007	Chronic kidney disease secondary to IgA nephropathy Modification of antiretroviral for abacavir, lamivudine, and efavirenz
September 2012	End-stage renal disease and initiation of dialysis
October 2012	Referral for a kidney transplantation evaluation
August 2013	Modification of antiretroviral therapy for abacavir, lamivudine, and raltegravir
October 2013	Listed on the kidney transplant waiting list
January 2016	Kidney transplantation from an HIV-positive donor Modification of antiretroviral therapy for abacavir, lamivudine, and dolutegravir Routine implantation biopsy at 7 days post transplantation showed no rejection
February 2016	Bacteremic graft pyelonephritis due to <i>Enterococcus faecalis</i>
August 2016	Excellent evolution post transplantation with good graft function and adequate control of HIV replication

and hemodialysis was initiated in 2012, time at which he was also evaluated for a kidney transplantation.

Clinical Findings

He was known for a resolved hepatitis B infection. His serology for hepatitis C was negative. Serologies for cytomegalovirus (CMV), varicella zoster virus, Epstein-Barr virus, and toxoplasmosis were consistent with past infections. The patient also suffered from coronary heart disease, atrial fibrillation necessitating long-term anticoagulation, hypertension, dyslipidemia, osteoporosis, and gout. He presented with *Staphylococcus aureus* bacteremia due to his arteriovenous fistula and recurrent *Clostridium difficile* colitis in late 2014. A defibrillator was installed in 2015 due to ischemic cardiomyopathy. During the pretransplant evaluation process, his antiretroviral regimen was switched to abacavir, lamivudine, and raltegravir in early 2013 to prevent potential future drug interactions with immunosuppressive medications. Plasma RNA HIV viral load had always been undetectable (<40 copies/mL) while on HAART, and the last plasma RNA HIV viral load prior to the transplantation had been done in December 2015.

Diagnostic Focus and Assessment

The donor was a 58-year-old man who suffered from cerebral hemorrhage and was declared neurologically deceased. He

had been diagnosed with HIV in 1995. His therapy consisted of abacavir, lamivudine, and dolutegravir since February 2015. His plasma RNA HIV viral load was consistently undetectable (<40 copies/mL) since 2011, and a resistance genotyping from 2010 showed a wild-type virus. The last plasma RNA HIV viral load available has been done in December 2015. His CD4 T-cell nadir was 370 cells/ μ L, and his last CD4 T-cell count was 440 cells/ μ L in December 2015. He had never developed any AIDS-defining illness. His serology for hepatitis B, hepatitis C, syphilis, and human T-lymphotropic virus were negative. The CMV serology was positive. There were 1 HLA-DR, 2 HLA-B, and 1 HLA-A donor-recipient mismatches. A pretransplant flow cytometry crossmatch was negative, and the recipient was donor-specific antibody-negative prior to transplantation. The donor had a serum creatinine of 44 μ mol/L, and his urine analysis revealed no proteinuria. Hence, the organ was accepted by the transplant physician without requesting a pretransplant biopsy.

Therapeutic Focus and Assessment

In January 2016, the patient received kidney transplantation from the HIV-positive donor. The surgery took place without complications, with a cold ischemia time of 264 minutes and a warm ischemia time of 45 minutes. Immunosuppression consisted of basiliximab (20 mg/d on days 0 and 4), tacrolimus (initiated at a dose of 0.05 mg/kg twice a day immediately before surgery and adjusted for target trough values in the range of 8-12 ng/mL), mycophenolate mofetil (720 mg postoperatively twice a day), and prednisone. A dose of cefazolin was given as wound infection prophylaxis before the surgery. Vancomycin per os was given for 7 days after transplantation for secondary prevention of *C difficile* colitis. The patient also received trimethoprim-sulfamethoxazole twice a week in prevention of *Pneumocystis jirovecii* pneumonia. As lymphocyte-depleting agents were not used, and since both the donor and the recipient were CMV positive, no anti-CMV prophylaxis was given. Immediately prior to transplantation, raltegravir was changed to dolutegravir to ensure adequate therapy for both the recipient and the donor's HIV strains. Hence, the recipient's antiretroviral therapy became abacavir, lamivudine, and dolutegravir.

The results of the implantation biopsy we routinely perform were available 7 days post transplantation and showed patchy, light to moderate arteriosclerotic lesions, global sclerosis in 15% of glomeruli, a focal and segmental sclerosis lesion in 1 glomerulus, light interstitial fibrosis and tubular atrophy, and a cellular crescent in 1 glomerulus with fibrinoid debris and erythrocytes in adjacent tubules. Light mesangial deposits of C3, IgM, kappa, and lambda light chains were described on immunofluorescence. The recipient had no follow-up biopsy given the need for anticoagulation due to his atrial fibrillation and stable graft function in the absence of urinary signs of glomerular disease.

Standard doses of tacrolimus as described above were used to obtain target trough levels. Levels were outside the target range on only 2 occasions, 1 of which was due to blood sampling a few hours after the morning dose of tacrolimus was taken. Except for these 2 instances, tacrolimus target trough levels were readily achieved in the absence of drug interactions.

The patient had an uneventful perioperative course, in the absence of acute rejection, delayed graft function, stenosis, lymphocele, infection, or leak. He was discharged on postoperative day (POD) 5 with a creatinine of 135 μ mol/L. On POD 18, the patient was admitted for bacteremic graft pyelonephritis due to *Enterococcus faecalis*. He was treated with piperacillin-tazobactam intravenously (IV) and switched to ampicillin IV for a total of 10 days. He was discharged on POD 24 but continued ampicillin per os until the removal of his ureteral stent on POD 42. Vancomycin per os for *C difficile* secondary prophylaxis was given from POD 18 to POD 47.

Follow-up and Outcomes

The patient is now doing well 6 months post transplantation. Plasma RNA HIV viral loads and CD4 T-cell counts have been monitored monthly. Plasma RNA HIV viral loads have remained undetectable (<40 copies/mL), and CD4 T-cell counts have remained over 300 cells/ μ L throughout follow-up. CMV viral loads have been followed weekly and have remained negative. Six months after transplantation, hepatitis B surface antigen (HBsAg) and hepatitis B virus DNA remain negative, with anti-HBs values >1000 U/L. On the last follow-up visit, serum creatinine was 155 μ mol/L, the urinary protein to creatinine ratio was in the normal range (0.02 g/mmol) and the patient had no hematuria.

Discussion

We report the first case of HIV-positive donor to HIV-positive recipient kidney transplantation in North America. Although kidney transplantation is now a well-accepted treatment for HIV-infected patients with ESRD, organ shortage and consequent prolonged waiting times remain problematic.⁷ This is especially true for HIV-infected patients, who fare worse than their noninfected counterparts on hemodialysis.⁶ One potential approach to decrease waiting time in HIV-positive transplant candidates is to use organs from HIV-positive donors, which would otherwise be discarded. In the past 5 years, our center has performed kidney transplantation in HIV-infected patients but always from HIV-negative donors. Main criteria for HIV-infected patient selection are CD4 T-cell count above 200 cells/ μ L, undetectable RNA HIV viral loads (<40 copies/mL), stable HAART for at least 3 months, and no untreatable opportunistic infection.¹

Current data on outcomes of HIV-positive to HIV-positive transplantation is reassuring. Muller et al initially reported 4

cases of kidney transplantation between HIV-positive donors and recipients in South Africa. Recipients needed to have undetectable plasma RNA HIV viral loads for 6 months on a stable antiretroviral regimen, and no history of previous opportunistic infection. Although the donors were antiretroviral-naïve, careful selection was based on no history of AIDS-defining illness.¹⁰ Baseline kidney biopsies were performed at the time of transplantation. In a recent report of 27 cases from the same group, patient and graft survival were similar in HIV-positive to HIV-positive kidney transplantations and HIV-negative to HIV-positive transplantations. Only deceased donors were included in the study.^{11,12} Muller and colleagues perform kidney biopsy as a baseline for reference; it does not affect the decision to accept the kidney (Elmi Muller, personal communication in written form, December 2016). Results of our routine implantation biopsy were available 7 days post transplantation. In addition to arteriosclerotic disease in the donor, 1 glomerulus showed a lesion compatible with crescentic, pauci-immune glomerulonephritis. The significance of this lesion remains unclear, given that neither the donor nor the recipient had urinary signs of glomerular disease.

For the first time, we chose to offer an organ from an HIV-infected donor to an HIV-positive candidate. This approach however raises concerns about the possibility of transmitting resistant HIV strain to the recipient. In our case, the donor's and the recipient's latest antiretroviral therapies were similar and based on an integrase inhibitor combined with abacavir and lamivudine. These therapies provided adequate sustained viral suppression in each patient. Immediately before transplantation, the recipient's antiretroviral therapy was switched to the donor's regimen, to ensure posttransplant virological control. In these conditions, we observed excellent plasma RNA HIV viral load control and steady CD4 T-cell count up to 6 months after transplantation.

HIV-positive to HIV-positive transplantation may lead to donor to recipient transmission of resistant strains, which could lead, in theory, to virological failure. Kidney allograft infection with HIV was reported in HIV-negative to HIV-positive kidney transplantation despite adequate viral suppression. Detection of urinary HIV RNA and DNA in HIV-infected patient with undetectable viremia raised the possibility that the kidney could act as an HIV reservoir.¹³ The impact of the viral burden within a donor's infected kidney on the risk of transmission is not clear and should be evaluated. Early changes related to HIV-associated nephropathy have reportedly developed in 3 kidney transplant recipients who have received organ from HIV-positive donors. Sequencing studies were not available. Although baseline biopsies showed no sign of nephropathy, these posttransplant changes could be caused by the donor's virus, the recipient's virus, or both.¹²

Superinfection and recombination of viral strains may occur in the presence of HIV dual infections. Cases of superinfection were reported in injecting drug users and in men who have sex with men.^{14,15} Superinfection was also reported in a patient with undetectable viremia.¹⁶ Studies revealed

conflicting results on the frequency of superinfection, owing to differences in the methodology of diagnosis, population characteristics, and HIV subtype. The most important clinical impact of superinfection would be the one leading to the acquisition of new resistance mutations. However, determining the cause of virological failure will be difficult, whether it is the result of a superinfection or the emergence of preexisting resistance undetected initially.^{17,18} Nonetheless, the risk of superinfection in solid organ transplantation is unknown. Undetectable viremia is needed prior to kidney transplantation; therefore, the risk of transmission should be negligible. According to the preliminary results of the Partner study, no transmission of HIV was reported in serodiscordant couples with adequate viral suppression.¹⁹

Drug interactions can increase the risk of acute rejection by creating unstable and subtherapeutic immunosuppressant concentration levels. Newer antiretrovirals such as integrase inhibitors show fewer interactions with immunosuppressive regimens. Our patient was on efavirenz before transplantation. Efavirenz is a nonnucleoside reverse-transcriptase inhibitor that induces cytochrome P450 3A4 that would lead to decreased circulating levels of tacrolimus, if the 2 were to be given concomitantly. To prevent this interaction, efavirenz was switched to raltegravir, an integrase inhibitor with no such potential interaction with tacrolimus, in anticipation of an eventual transplantation. Raltegravir was switched to dolutegravir, another integrase inhibitor without potential interactions with tacrolimus, at the time of transplantation to be consistent with the donor's therapy.

Our case illustrates that successful HIV-positive to HIV-positive kidney transplantation can be performed without loss of virological control. We undertook the procedure in ideal conditions, given the full knowledge we had of both the donor's and the recipient's HIV strains, complete genotypic data, and previous virological control and therapy. Results may be different when either information on the latter is lacking or when donors have resistant strains. In the absence of data, the decision to proceed with transplantation will continue to be made on an individual basis, weighing the urgency of the procedure, especially in the case of transplantation of life-saving organs against the potential risk of loss of HIV replication control. The favorable posttransplant course we report suggests that the donor pool for HIV-positive patients with ESRD can be expanded through the use of organs from HIV-positive donors. Given the documented benefit of kidney transplantation for HIV-positive patients with ESRD and their inferior survival on dialysis compared with HIV-negative patients, this represents a promising avenue to improve longevity and quality of life in this patient population.

List of Abbreviation

CHUM, Centre Hospitalier de l'Université de Montréal; CKD, chronic kidney disease; CMV, cytomegalovirus; CrCHUM, Centre de recherche du Centre Hospitalier de l'Université de Montréal; ESRD, end-stage renal disease; HAART, highly active antiretroviral

therapy; HIV, human immunodeficiency virus; POD, postoperative day; UHRESS, Unité hospitalière de recherche et d'enseignement sur les soins sur le SIDA.

Ethics Approval and Consent to Participate

Ethics approval was obtained from CrCHUM Ethics Board (CÉR-CHUM 15.344) and patient consented to the study (Cohorte prospective des patients infectés par le VIH en évaluation pré-transplantation d'organes solides (TOS) ou transplantés d'organes solides).

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report.

Availability of Data and Materials

Will be made available on request.

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Declaration of Conflicting Interests

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