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Brief Communication

Report of Four Simultaneous Pancreas–Kidney Transplants in HIV-Positive Recipients with Favorable Outcomes

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The advent of combined antiretroviral therapy (cART) dramatically changed the view of human immunodeficiency virus (HIV) infection as an exclusion criterion for solid organ transplantation, resulting in worldwide reports of successful transplants in HIV-infected individuals. However, there are few reports on simultaneous pancreas–kidney transplant in HIV-positive recipients detailing poor outcomes. A series of four pancreas–kidney transplant performed on HIV-infected individuals between 2006 and 2009 is presented. All recipients reached stably undetectable HIV-RNA after transplantation. All patients experienced early posttransplant infections (median day 30, range 9–128) with urinary tract infections and bacteremia being most commonly observed. In all cases, surgical complications led to laparotomic revisions (median day 18, range 1–44); two patients underwent cholecystectomy. One steroid-responsive acute renal rejection (day 79) and one pancreatic graft failure (month 64) occurred. Frequent dose adjustments were required due to interference between cART and immunosuppressants. At a median follow-up of 45 months (range, 26–67) we observed 100% patient survival with CD4 cell count $>$300 cells/mm^3 for all patients. Although limited by its small number, this case series represents the largest reported to date with encouraging long-term outcomes in HIV-positive pancreas–kidney transplant recipients.

Key words: HIV infection, pancreas and kidney, transplant, outcomes

Abbreviations: AIDS, acquired immunodeficiency syndrome; cART, combined antiretroviral therapy; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CSA, cyclosporine A; EBV, Epstein Barr virus; ESRD, end-stage renal disease; HBV Hepatitis B virus; HCV, Hepatitis C virus; HHV6, Human herpesvirus 6; HHV8, Human herpesvirus 8; KT, kidney transplant; IVDU, Intravenous drug users; MMF, mycophenolate mofetil; PI, protease inhibitor; SOT, solid organ transplantation; SPK, simultaneous pancreas–kidney transplantation; SRL, sirolimus; TAC, tacrolimus; TB, tuberculosis; UTI, urinary tract infection.

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Introduction

The introduction of combined antiretroviral therapy (cART) revolutionized the concept of human immunodeficiency virus (HIV) infection as an exclusion criterion for solid-organ transplant (SOT) eligibility (1). In the past decade, an escalating number of HIV-infected recipients have been reported in case series worldwide with outcomes comparable to those in the HIV-negative population (2,3). A recent prospective study encompassing 150 kidney-transplant (KT) recipients in an HIV cohort reported survival rates of 94.6% and 88.2% at 1 and 3 years posttransplantation, respectively (3).

Kidney transplantation proved to be a valid therapeutic approach in HIV-infected patients displaying higher survival rates compared to patients remaining on dialysis (2–4). Although simultaneous pancreas–kidney transplant (SPK) represents the only proven long-term therapeutic approach for diabetic patients having progressed to end-stage renal disease (ESRD), the incidence of SPK complications remains high and represents a major limiting factor to endorsement in HIV-positive recipients (5). Two cases of SPK have been reported in HIV-positive recipients to date showing poor outcomes (6,7). Although limited by its small size, the case series reported herein is the largest reported to date with 100% survival rates, suggesting that encouraging long-term outcomes can be achieved in HIV-positive SPK recipients.

Materials and Methods

Records from files of four HIV-positive SPK recipients were prospectively collected between January 2006 and July 2011. A computerized SPSS system (version 15; SPSS Inc., Chicago, IL, USA) was used for data collection and analysis. Patients' data were expressed as median plus range or as mean ± SD values. All patients received an organ from a deceased donor and underwent SPK. Left iliac fossa and right retroperitoneal space were chosen for kidney and pancreas placements, respectively. The pancreas was implanted using venous drainage into inferior vena cava and enteric exocrine drainage.

Inclusion criteria for SOT in HIV-infected recipients

In 2003, the Italian National Transplantation Centre approved the protocols for KT and SPK in HIV-infected recipients. The protocol accounted for standard-of-care HIV-infection related pretransplant inclusion criteria (Table S1; Ref. 8). The possibility to receive an organ from increased risk donors was offered to all patients through an exhaustive protocol explanation and the signature of a dedicated informed consent form at the time of listing and organs' availability (9,10).

Immunosuppressive therapy

Immunosuppression consisted of basiliximab induction (20 mg on the day of transplant and on postoperative day 4) followed by maintenance with tacrolimus (TAC; 0.1 mg/kg twice a day), mycophenolate mofetil (MMF; 1 g twice a day) and prednisone. Following an initial 250 mg IV methylprednisolone on the day of transplantation, and 125 mg on day 1, the dose was decreased to 16 mg of oral prednisone daily and subsequently tapered. Steroid withdrawal was undertaken, when possible, within the 3rd month after transplantation (11). TAC blood levels were regularly monitored (12) and drug doses adjusted accordingly to maintain trough levels between 8 and 15 ng/mL during the first 3 months and between 5 and 10 ng/mL thereafter. Cyclosporin A (CSA) was used following transplantation in one patient. In one case of biopsy-documented, TAC-related toxicity, sirolimus (SRL) at a starting dose of 3 mg daily was employed.

Antiretroviral therapy

cART was discontinued immediately before the transplant and then reintroduced according to patients' condition and HIV viral load. cART was changed in instances of antiretroviral-related side effects or interference with immunosuppressants. Monitoring of antiretroviral plasma levels was performed in cases of known interference with immunosuppressants.

Management of rejection

Renal or pancreatic biopsies were performed in cases of persistent elevation of serum creatinine and/or amylase and lipase, respectively. Biopsies were assessed for infection, recurrent disease, calcineurin inhibitor (CNI) toxicity and acute organ rejection. Allograft nephropathy was scored according to Banff's criteria (13). Acute rejections were treated with IV methylprednisolone boluses (500 mg/day for 3 days). Antidonor alloantibodies were tested (Luminex Corporation, Austin, TX, USA).

Prophylaxis and posttransplant follow-up

Surgical prophylaxis consisted of perioperative administration of ampicillin/sulbactam (3 g IV at induction, then 1.5 g every 12 hours) and fluconazole (400 mg IV) continued for 24–48 h after the intervention (14). Cotrimoxazole was used for *Pneumocystis jiroveci* infection prophylaxis and discontinued at 6 months posttransplant if absolute CD4 count $\geq$200 cells/mm^3 was achieved. At our institution, cytomegalovirus (CMV) preemptive therapy was administered only if CMV-DNA in whole blood was found on the basis of regular blood monitoring above the cut-off of 100 000 copies/mL, regardless of pretransplant CMV serostatus (15).

A multidisciplinary transplant team (cART and transplant infectious diseases experienced specialists, surgeons, nephrologists, endocrinologists, virologists, pharmacologists, radiologists and microbiologists) performed posttransplant surveillance. HIV status monitoring included measurement of plasma HIV-RNA levels and absolute CD4 cell count and percentage twice a week during the first month, followed by monthly follow-up and subsequently every 3 months. Serum creatinine, glucose, pancreatic amylase and lipase, C peptide, and glycosylated hemoglobin were monitored monthly. HHV8 DNA was also performed in case of positive donor or recipient serology due to HHV8 high prevalence in certain areas of Italy. Posttransplant follow-up schedule is summarized in Table S2. In cases of positive HCV-antibody and HCV-RNA levels, a liver biopsy was performed at the time of listing to rule out advanced liver disease, and HCV-RNA and liver function tests were monitored every 6 months.

Results

Patients' characteristics

Patients' characteristics are summarized in Table 1. All patients (3 males, 1 female) were HIV-infected type 1 diabetics with chronic renal disease on hemodialysis. The median age was 39.5 years (range 31–49). Ethnicity was Caucasian except for the female recipient (Patient 3) who was of African origin. The median duration of HIV infection estimated from the time of first HIV-positive test was 7.5 years (range 3–19). Risk factor for HIV transmission was sexual in 3 patients. Patient 2, naive to antiretrovirals due to stability of immunovirological parameters, was a previous intravenous drug user (IVDU), genotype 1 HCV coinfected with HCV-RNA positivity, and had no fibrosis at liver biopsy (Ishak grade II, stage 0). Overall dialysis duration before SPK was 4 years (1391 days, range 542–2607) with a time spent on the transplant waiting list of around 123 days (range, 84–520). Average absolute CD4 cell count measured within 3 months before transplant was 534 cell/mm^3 (range 470–698). Patients 1 and 4 received organs from standard risk donors, Patient 3 from an increased risk donor, and Patient 2 from a donor with calculated risk for bacteremia, as defined by the Italian guidelines (9,10). The average donors' age was 29 years (range 23–39). Median cold ischemia time was 13.5 h (range 9–16). All recipients were CMV-IgG and EBV-IgG positive. Patients 2 and 3 serology was compatible with previous Hepatitis B virus (HBV) infection. We registered one immune response to HBV vaccination (Patient 4, HBsAb 1000 mUI/mL) in the two HBsAg-, HBcIgG-negative recipients.

Posttransplant follow-up and graft survival

Overall posttransplant follow-up ranged from 2 to 5 years with a median duration of 45 months (range 26–67). As reported in Table 1, all patients had stable creatininemia at last follow-up visit (median 1.24 mg/dL, range 1.20–1.28). Glucose levels were within normal range in 3 of 4 recipients (86 mg/dL, range 75–99). Patient 1, presently back on insulin therapy because of pancreatic graft loss and under evaluation for islet transplantation, presented with fever and hyperglycemia (429 mg/dL) at posttransplant month

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Table 1: Clinical characteristics of HIV-positive recipients of simultaneous pancreas–kidney transplantation (SPK) and posttransplant follow-up

Recipients characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	35	44	31	49
cART	Stavudine, lamivudine and nelfinavir	None	Emtricitabine, nevirapine and atazanavir-ritonavir	Stavudine, lamivudine and efavirenz
CD4 count (%) (cells/mm^3)	470 (39)	470 (16)	698 (33)	598 (26)
HIV-RNA (copies/mL)	<50	80 000[1]	<50	<50
Posttransplant follow-up	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**
cART restart (days)	25	58	27	41
cART	Zidovudine, lamivudine and efavirenz	Lamivudine, abacavir and fosamprenavir-ritonavir	Lamivudine, abacavir and atazanavir-ritonavir	Lamivudine, abacavir and raltegravir
HIV-RNA < 50 cp/mL after cART (days)	93	195	123	71
Stable CD4 count ≥ 200 cells/mm^3 (days)	97	46	74	112
TAC average dose pre-cART (mg/day)	6	5	4.3	5
TAC average trough level pre-cART (ng/mL)	20	17.1	12.2	16.4
TAC average dose post-cART[2]	5 mg/day	0.5 mg/week	1 mg/week	6 mg/day
TAC average trough level post-cART (ng/mL)[2]	7.1	13.3	13.5	6.6
Serum creatinine (mg/dL)[3]	1.28	1.20	1.24	1.23

[1]Patient naive to cART.
[2]Values within 3 months post-cART.
[3]Values at last follow-up visit.

64. During routine follow-up 1 month before hospitalization, results were within normal limits. An abdominal CT scan showed possible pancreatic graft vascular thrombosis not confirmed at laparotomy that evidenced a necrotic pancreatic graft with patent vessels and was followed by graft removal. Histologic examination displayed signs of necrotic acute pancreatitis associated with acute and chronic rejection.

All recipients had undetectable HIV-RNA at last follow-up visit. Mean absolute CD4 number and percentage were 425 cells/mm^3 (range, 307–701) and 28% (range 23–29%), respectively. Patient 2, who had a negative pretransplant tuberculin skin test (TST) and negative history of tuberculosis (TB) exposure, developed pulmonary TB 35 months after transplantation and was successfully treated with an 18-month course of a rifamycin-sparing antimycobacterial treatment (16). No acquired immunodeficiency syndrome (AIDS) defining illnesses were reported among the other recipients. Patient 3 presented genital HSV-2 reactivation at posttransplant day 19 and was treated with oral valacyclovir. No preemptive CMV treatments were started given that the highest CMV-DNA viral load registered was 31 000 copies/mL. Before SPK, HHV8 serology was negative for all the donors and for two of the recipients. HHV8 serological status was not available for the other two recipients. All recipients were negative for HHV8-DNA (undetectable by PCR) and no lesions suggestive of Kaposi's sarcoma were observed during posttransplant follow-up.

Renal and pancreatic function

C peptide and glycosylated hemoglobin levels were maintained within normal range in all recipients. Patient 1 presented an increase in amylase and lipase levels at posttransplant month 18 (up to 541 UI/L and 1185 UI/L, respectively). Pancreatic biopsy reported moderate chronic pancreatitis interpreted as possible MMF toxicity and resolved within 5 months after MMF discontinuation. CNI-related toxicity before cART reintroduction was advocated by renal biopsy for Patient 3 and 4 and accompanied by a creatinine increase of 2.24 and 3.69 mg/dL (posttransplant day 7 and 22), respectively. Patient 3 was on IV CSA-based regimen (trough levels of 301 ng/mL), and Patient 4 was receiving a TAC (trough levels of 17.4 ng/mL). Patients 3 and 4 were switched to TAC and SRL, respectively. Subsequently (posttransplant day 30) Patient 3 presented a creatinine increase (2.46 mg/dL) associated with the presence of detectable donor-specific anti-HLA alloantibodies in the serum. TAC levels were 13.7 ng/mL. In absence of other possible causes of renal damage, a course of IV immune globulin was attempted and followed by creatinine normalization at day 4 after treatment.

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Acute rejection

Patient 4's renal biopsy showed acute cellular rejection (Banff stage 2A) at posttransplant day 79. Methylprednisolone boluses administration was followed by creatinine decrease from 2.71 to 1.61 mg/dL. The rejection was related to efavirenz reintroduction causing SRL level reduction (from 7 to 3.9 ng/mL). Efavirenz blood levels were within normal limits. Due to difficulty in achieving target trough levels despite increasingly higher SRL doses (up to 7 mg daily), the treatment was switched to TAC and raltegravir replaced efavirenz.

HIV status, cART and immunosuppression

Pre- and post-SPK cART are listed in Table 1. Pretransplant genotypic testing was available only for Patients 3 and 4 and did not show any major antiretroviral mutations. Antiretrovirals were discontinued on the day of SPK. HIV-RNA was detectable in all recipients at median day 28 (range 25–31), except for Patient 2 who had positive HIV-RNA before transplant. cART was reintroduced shortly after positive plasma HIV-RNA detection. At median day 108 after cART reintroduction (range 71–195), HIV-RNA returned stably to undetectable levels. Figure 1 shows HIV-RNA viral load and absolute CD4 cell count trends during the first 2 years posttransplant. Initially, low or undetectable HIV-RNA was reported in almost all recipients, followed by a rebound of viral replication successfully controlled by all patients after cART reintroduction. The overall CD4 cell count, affected by the immunosuppressant therapy in the early posttransplant, trended upward for all recipients. Median CD4 percentage was 22% (range 16–28%) in the first 12 weeks posttransplant and 25% (range 20–33%) from week 12 up to week 48 posttransplant. Recipients receiving PI-based cART required much lower TAC doses compared to Patients 1, on an NNRTI-based regimen, and Patient 4, on raltegravir. Prednisone was discontinued in 3 of 4 patients within the first 3 months after transplantation (median day 92, range 25–219 days) with no consequences on graft function. Patient 1 was the first transplanted, when an early steroid withdrawal policy was not yet routinely established at our center. Two steroid discontinuation attempts after posttransplant month 6 were followed by creatinine increases (maximum serum level of 2.18 mg/dL). At posttransplant month 19, a borderline rejection (renal biopsy showing lymphocyte infiltration <10% and rare intratubular $CD3^+$ cells) was documented with maximum creatinine levels of 2.17 mg/dL and followed by normalization in absence of therapy. The patient is currently maintained on prednisone 2 mg/day.

Posttransplant complications

Posttransplant complications are listed in Table 2. Surgical complications and posttransplant infections mostly occurred within the first 4 weeks posttransplant, at median days 18 (range 1–44 days) and 30 (range 9–128 days), respectively. Most common infections were urinary tract

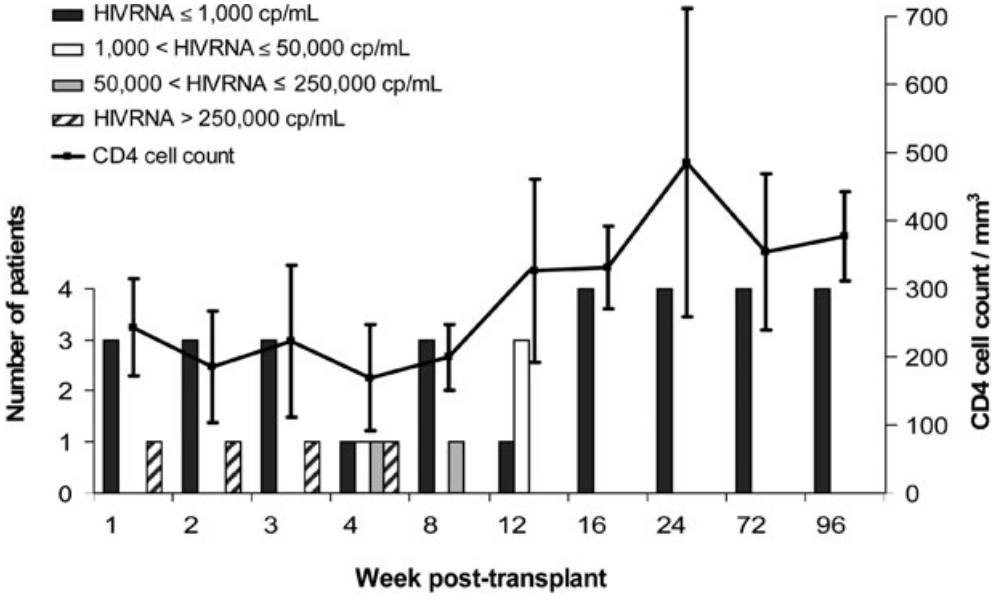

Figure 1: HIV-RNA and CD4 absolute cell count trends in the HIV-positive recipients of simultaneous pancreas–kidney transplant (SPK). HIV-RNA levels, expressed as copies/mL (cp/mL), and absolute CD4 cell count (average ± SD), expressed as cells/mm^3, are reported up to 24 months posttransplant. HIV-RNA levels were measured at various time points and grouped in four categories (1) ≤ 1000 copies/mL, (2) 1000 < cp/mL ≤ 50 000, (3) 50 000 < cp/mL ≤ 250 000 and (4) >250 000 cp/mL. With the exception of Patient 2, naive to cART with detectable HIV-RNA at baseline, all recipients maintained low or undetectable HIV-RNA for the first 3 weeks posttransplant. All patients reached undetectable HIV-RNA levels within posttransplant week 16. Average absolute CD4 cell count trended upward during the posttransplant follow-up, remaining stable above 300 cells/mm^3 starting from posttransplant week 12.

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Table 2: Posttransplant complications in HIV-positive recipients of simultaneous pancreas-kidney transplantation (SPK)

Type	Patient	Number of episodes	Posttransplant day	Management
Surgical				
Bleeding	Patient 1	1	9	Blood transfusion,
	Patient 2	1	1	laparotomy,
	Patient 3	3	1, 14, 44	embolization
Hematoma	Patient 1	1	33	Laparotomy,
	Patient 3	2	8,33	drainage
Cholecystitis	Patient 2	1	26	Cholecystectomy
	Patient 4	1	9	
Infectious	Patient	Number of episodes	Posttransplant day	Isolation
Abscess	Patient 1	1	27	*E. coli*
	Patient 2	1	26	None
	Patient 3	1	33	*MRSA, P. aeruginosa*
UTI	Patient 1	2	52, 128	*E.coli*
	Patient 2	2	43, 61	*E. coli*
	Patient 3	1	67	*K. pneumoniae*
Wound infection	Patient 4	1	12	*E. faecalis*
Bacteremia	Patient 1	1	9	*E. coli*
	Patient 3	3	11, 14, 33	*MRSA, P. aeruginosa*
Pneumonia	Patient 1	2	13, 1050	None

infections (UTIs) and bacteremias. All SPK recipients suffered surgical complications leading to laparotomic interventions, with an average of two surgical revisions per patient. Three patients experienced anastomotic bleeding (median posttransplant day 9, range 1–44 days). In Patient 1 and 3, hematomas formation required surgical drainage. Two patients underwent cholecystectomy due to gangrenous cholecystitis at posttransplant day 26 and day 9, respectively. Association of surgical complications with infectious processes occurred in three patients: a subdiaphragmatic abscess, a pelvic abscess subsequent to a complicated cholecystitis and an infected psoas hematoma. Patients 1 and 3 experienced episodes of bacteremias, with *Escherichia coli*, *Pseudomonas aeruginosa* and *MRSA* as the most commonly isolated pathogens. Three patients had recurrent UTIs. Surgical site infection due to *Enterococcus faecalis* was documented in Patient 2 (posttransplant day 12). One episode of pneumonia (posttransplant day 13) and one pulmonary TB infection, as described (16), were also reported.

Discussion

Coexistence of type 1 diabetes in HIV-infected patients is a minor cause for ESRD (17). Nevertheless, the association of insulin dependency, dialysis-related risks and HIV disease poses serious mortality hazards. Survival rates up to 85 and 68% at 5 and 10-years posttransplant have been reported for HIV-negative SPK recipients (18). Because today the cumulative survival of HIV-positive individuals does not dramatically differ from the non-HIV population, SPK can be reasonably considered a valid treatment for HIV-positive recipients, provided that therapeutic options to control viral replication are available (1). To our knowledge, only two reports of SPK were described in HIV-infected recipients documenting a case of early pancreatic graft loss due to venous thrombosis and death from *P. aeruginosa* infection, and one case of chronic rejection with late renal and pancreatic graft failure (6,7). Major challenges of SPK are surgical complications, infections and graft rejections (18). In particular, we registered two cases of complicated cholecystitis. Compared to the general population, a higher prevalence of biliary disease has been reported in SPK type 1 diabetic patients (28% vs. 10–15%; Ref. 19). Our data support a regular sonographical posttransplant follow-up and suggest that elective cholecystectomy may be considered in HIV-infected SPK recipients. Posttransplant infection rates did not seem to be different from the HIV-negative population (18). All patients who underwent SPK achieved undetectable HIV viral load at a median time of 12 weeks after cART reintroduction and their absolute CD4 cell count recovered. cART was restarted in concomitance with viral replication; CD4 cell count decline in the early posttransplant period, instead, may represent a confusing parameter to guide cART restart due to the impact of immunosuppressive regimens on T-cell number. Furthermore, the antiretroviral-free status during the first weeks after transplantation could reduce drug interactions favoring the achievement of appropriate immunosuppressant levels. Risks of CNI toxicity, transplant rejection, or HIV rebound relate to the delicate balance between immunosuppressants and antiretrovirals (2,3,20). In cases of regimens containing protease inhibitors (PI), high-circulating levels of immunosuppressants likely favors CNI-related toxicity early posttransplant (i.e. prolonged effect of PI-based pretransplant cART discontinued at induction of immunosuppression). Conversely, efavirenz-based regimens may induce subclinical immunosuppressive levels, leading to graft rejection. Thus, the expertise in cART use is

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mandatory in managing HIV-positive recipients. The choice of regimens including antiretrovirals that do not interfere with immunosuppressants' metabolism (i.e. raltegravir) should be considered when possible and may provide in the early posttransplant an alternative option to cART interruption to avoid uncontrolled HIVRNA rebound (7,20). Higher incidence of graft rejection rates in HIV-positive recipients compared to HIV-negative recipients have been reported but are conflicting (2,3). We observed one case of acute cellular rejection related to pharmacological interference and one late pancreatic graft failure with maintenance of intact renal function. The causes of pancreatic graft loss were ascribed to a nonvascular acute dysfunction superimposing fibrotic graft progression.

Long-term steroid-mediated immunosuppression has been associated with higher mortality in transplant recipients and its discontinuation has not determined higher rejection rates (11). Our experience did not show any impact of steroid withdrawal on patients and grafts survival.

The chronicity of HIV disease and the consequent increase of end-stage organ diseases and cART-related complications (i.e. glucose intolerance, heart diseases) will likely increase the request for SOT 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 cART regimens. Although limited by its size, our series represents the largest reported for SPK HIV-positive recipients documenting promising results. We believe that the use of standardized protocols along with the careful management of antiretrovirals and immunosuppressants and a close patient's follow-up were crucial factors in achieving positive results in HIV-positive patients undergoing SPK.

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Disclosure

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

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Supporting Information

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

Table S1: Inclusion and exclusion criteria for kidney–pancreas transplantation (SKP) in HIV-infected recipients.

Table S2: Posttransplant follow-up schedule for simultaneous kidney–pancreas transplant (SKP) in HIV-positive recipients up to 24 months.

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