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Clinical outcome of kidney transplantation in HIV-infected recipients: a retrospective study

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Abstract

Kidney transplantation is a safe and effective option for HIV-positive (HIV^+) patients. We conducted a retrospective study on HIV^+ kidney transplant recipients who underwent transplantation from March 2008 to September 2016. Inclusion criteria for transplantation were CD4+ T-cell count $\geq$200 per mm^3 and undetectable HIV load. The current study reports the outcome of 19 HIV^+ recipients, mostly of Caucasian origin (79%) with a median age of 50 years (interquartile range [IQR], 42–52), who were followed up for a median period of 2.4 years (IQR, 1.2–4.6) after transplantation. Compared with HIV-negative (HIV^-) controls, HIV^+ recipients had similar one- and three-year graft and patient survival, but significantly lower five-year patient survival ($P = 0.03$). The differences in graft outcome became less evident with the analysis of death-censored graft survival rates. Cumulative incidence of allograft rejection at one year was 32.9%. Rates of infections were not particularly elevated and HIV replication remained well controlled in all but one patient. A high prevalence of metabolic and endocrine complications (68%) was reported after transplantation. Further studies are needed to evaluate long-term outcomes of HIV^+ recipients who underwent kidney transplantation.

Keywords
HAART, transplantation, Europe, HIV

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Introduction

HIV infection continues to be a major public health challenge worldwide. Despite a slight reduction of incidence, global prevalence of HIV tends to increase steadily as people on antiretroviral therapy live longer.[1–3] Although the advent of highly active antiretroviral therapy (HAART) has substantially improved morbidity and mortality of HIV-positive (HIV^+) patients,[4–6] the prevalence of comorbidities has increased with increasing prevalence of people living with HIV. End-stage renal disease (ESRD) is one of the most serious complications[7] and a leading cause of death[8] in patients infected with HIV. Kidney transplantation has been considered the best renal replacement treatment option for HIV^+ patients reaching ESRD as it is safe and effective; moreover, it is associated with an increase in life expectancy.[9] Key factors for a successful kidney transplantation rely essentially on the beneficial effect of HAART[5,10] and the absence of detrimental effects of immunosuppressive therapy on HIV progression. Over the years, several studies have shown excellent patient and graft survival rates, similar to uninfected kidney transplant (KT) recipients.[9,11–14] However, the interpretation of these data

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is limited principally by short-term follow-up (less than five years) of the above-mentioned studies, which should not be considered as representative for long-term outcomes in this vulnerable population.

Since we are aware that several risk factors may negatively influence long-term patient and graft survival of HIV^+ KT patients, we conducted an observational study aimed at describing the clinical outcomes of these patients.

Methods

This retrospective study was conducted at the University Hospital of Modena, an active renal transplant center that started a program of kidney transplantation of HIV^+ patients from HIV-negative (HIV^-) deceased donors in 2008. The eligibility criteria for kidney transplantation were as follows: (i) CD4+ T-cell count consistently $\geq$200 cells/mm^3 in patients not on antiretroviral therapy (monitoring of CD4+ T-cell count every three months); (ii) undetectable HIV viral load (VL) (<50 HIV-1 RNA copies/mL) and CD4+ T-cell count $\geq$200 cells/mm^3 for at least six months in patients on antiretroviral therapy; and (iii) presumed good compliance to follow-up and therapy.

We collected and reviewed all data of HIV^+ KT recipients from March 2008 to September 2017, date of last follow-up. The study was approved by Institutional Review Board of the University of Modena and Reggio Emilia.

Immunosuppressive therapy

All recipients received induction therapy with a monoclonal anti-interleukin 2 receptor antibody (Basiliximab) at a dose of 20 mg on postoperative days (POD) 1 and 4.

Two different immunosuppressive protocols were used as maintenance therapy. From March 2008 to March 2015, immunosuppressive strategy was based on calcineurin inhibitor minimization including low dose of cyclosporine (Cys), everolimus (EVL) and steroid (methylprednisolone). In the early post-transplant period, Cys dose was adjusted to achieve a 2-h postdose Cys level (C2) of 1000–1200 ng/mL. EVL was introduced on POD 21. During the first six months after kidney transplantation, C2 and target trough level of EVL were maintained at 400–500 ng/mL and 8–10 ng/mL, respectively, and were tapered, respectively, to 250–350 and 6–8 ng/mL after six months. From April 2015, the maintenance immunosuppression of new HIV^+ KT recipients included tacrolimus (TAC), mycophenolic acid (MPA) and steroid (methylprednisolone). TAC was given when creatinine was <3.0 mg/dL; dose was adjusted to achieve target trough level of 10–12 ng/mL. During the first six months after KT, target trough level of TAC was maintained at 8–10 ng/mL and then was tapered to 6–8 ng/mL.

Methylprednisolone was given as follows: 500 mg intravenously at POD 0, 250 mg at POD 1, 125 mg at POD 2 and 80 mg at POD 3. From POD 4, oral prednisolone (16 mg/day) was tapered progressively until 4 mg/day at the sixth month.

The dose of MPA (360 mg three times daily) was adjusted according to gastrointestinal tolerability, risk of infectious diseases and laboratory parameters.

Infectious disease prophylaxis

Patients received trimethoprim-sulfamethoxazole or pentamidine isethionate for *Pneumocystis jirovecii*, at least for 12 months. According to the institutional protocol, intravenous (IV) ganciclovir or oral valganciclovir were given for cytomegalovirus (CMV) prophylaxis to all patients regardless of donor/recipient serology matching for 12 months. Ganciclovir was administered for the entire length of hospital stay and then was replaced by oral valganciclovir. From 2010, valganciclovir was the first-line therapy of CMV prophylaxis in our Center. In case of a CMV-positive donor and a CMV-negative recipient, anti-CMV immunoglobulin (Ig) was also administered. CMV, Epstein-Barr virus (EBV), and human herpes virus (HHV) 6, HHV-8, polyomavirus BK and JC virus were monitored according to the Italian National Kidney Transplant Program guidelines.[15]

Diagnosis and treatment of acute rejection

Rejection was suspected by a delayed graft function, rapid increase in serum creatinine concentration (more than 15%) and new onset or progressive worsening of proteinuria (approximately > 1 g/day). Anti-HLA antibodies testing was performed whenever rejection was suspected. Biopsy-proven acute T-cell-mediated rejection (TCMR) was treated with IV pulse of methylprednisolone (250–500 mg daily for three days). Biopsy-proven antibody-mediated rejection (AMR) was treated with a combination of plasmapheresis ($\geq$7 sessions), rituximab (375 per square meter of body-surface area weekly for four weeks) and high dose IV Ig (2 g/kg); in case of mixed acute rejection, IV methylprednisolone was added at a dose of 250–500 mg daily for three days.

Management of HIV infection

An infectious diseases consultant with expertise in HIV disease managed prescription and monitoring of antiretroviral agents. HAART was given in the immediate postoperative period. Pre-transplant resistance profile

was obtained from patient history or analyzing HIV DNA from lymphocytes if the patients had undetectable HIV RNA loads. Antiretroviral regimens were selected in order to maintain an undetectable VL, prevent interactions with immunosuppressive drugs and avoid undesirable side effects such as nephrotoxicity (Table 2). Treatment was chosen on the basis of drug product availability, HIV pre-transplant genotype profile, individual drug tolerability, hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection and comorbidities.

Clinical outcomes

Measured outcomes included patient and graft survival; cumulative incidence of acute rejection episodes; HIV immuno-virological response (HIV RNA VL, CD4+ T-cell count, and CD4/CD8 ratio); and prevalence of metabolic disorders, neoplasms, and serious infections. In our Center, undetectable HIV VL was defined as an HIV RNA level lower than 40 copies/mL.

Patient and graft survival rates at one, three, and five years in HIV^+ patients were compared with two cohorts (entire population and patients aged $\geq$65 years) of HIV^- patients who underwent single kidney transplantation from deceased donor at our Center during the same period (from January 2008 to September 2016). Assessment of kidney function was performed by estimated GFR using the CKD-EPI equation.[16] Graft loss was defined as return to dialysis or death with a functioning graft. Delayed graft function (DGF) was defined as the need of hemodialysis during the first post-transplant week. Serious infection event was defined as infection requiring hospitalization. Diagnosis of HCV infection was made by detection of HCV RNA at the end of follow-up.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges (IQRs); ordinal variables and data about doses of immunosuppressive agents (Table 2) are presented as means $\pm$ SD. Prevalence was expressed as percentages.

Kaplan–Meier curves were used to calculate patient and graft survival, whereas Wilcoxon–Mann–Whitney test and analysis were used to evaluate differences in age among HIV^+ patients and HIV^- controls. Death-censored graft survival was calculated from the date of transplantation to the date of last follow-up if graft was still functioning, or the date of graft failure. Statistical analysis was performed using the GraphPad Prism 6® software.

Results

Patients and donors characteristics

We enrolled 19 HIV^+ patients who underwent kidney transplantation from deceased donors. Recipients and donors characteristics are presented in Table 1.

The median age of recipients was 50 years (IQR, 42–52 years). The majority of the subjects were male (n = 11, 68%) and of Caucasian origin (n = 15, 79%). KT recipients were followed up for a median of 2.4 years (IQR, 1.2–4.6 years). At the time of the analysis,

Table 1. Baseline characteristics of donors and HIV^+ KT recipients.

Donor (n = 19)	
Age—yr	
Median (IQR)	39 (25–43)
Deceased—no. (%)	19 (100)
High infectious risk—no. (%)	7 (37)
Expanded criteria—no. (%)	1 (5)
CMV seroprevalence—%	82
Recipient (n = 19)	
Age—yr	
Median (IQR)	50 (42–52)
Male sex—no. (%)	13 (68)
Race—no (%)	
White	15 (79)
Black	3 (16)
Other	1 (5)
Cause of chronic kidney disease—no. (%)	
Unknown	8 (42)
Presumed HIV-associated nephropathy	2 (10)
Chronic pyelonephritis	2 (10)
Membranous glomerulonephritis	2 (10)
Other causes	5 (28)
Dialysis vintage—yr	
Median (IQR)	4.3 (2.8–5.7)
Time on waiting list	
Median	0.8 (0.3–1.2)
PRA > 80%—no. (%)	3 (16)
HLA mismatch	
Mean	3.5
Time since HIV diagnosis—yr	
Median (IQR)	15.7 (12.6–23.1)
CD4 T-cell count—cells/mm^3	
Median	407 (367–556)
CD4/CD8 ratio	
Median (IQR)	0.64 (0.46–0.96)
CMV seroprevalence—%	
EBV seroprevalence—%	95
HCV infection (RNA detectable)—no. (%)	100
HBV infection (DNA detectable)— no. (%)	2 (10)
Patient on HAART—no. (%)	19 (100)

EBV, Epstein–Barr virus; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, Hepatitis C Virus; HLA, human leukocyte antigens; IQR, interquartile range; and PRA, panel reactive antibody.

five patients had completed at least five years of follow-up. No patient was lost to follow-up.

Slightly less than half of patients (n = 8, 42%) had ESRD of unknown origin. Kidney transplantation was performed after a median age of 15.7 years (IQR, 12.6–23.1 years) from the diagnosis of HIV. Median dialysis vintage was 4.3 years (IQR, 2.8–5.7 years) and median time on waiting list was 0.8 years (IQR, 0.3–1.2 years). The median cold ischemia time was 15.8 h (range, 12.2–20 h).

According to local protocol, in the early postoperative period, 11 KT recipients received an immunosuppressive treatment including low-dose Cys, EVL, and steroid. From 2015, eight patients received TAC, MPA, and steroid. Table 2 summarizes the dose adjustments of all the immunosuppressive drugs within five years following transplantation.

The median age of HIV^- KT recipients was 52 years (IQR, 43–60 years); older recipients (age $\geq$65 years) had a median age of 68 years (IQR, 66–70 years). Whereas there were no significant differences in ages between HIV-infected and the entire uninfected population (P = 0.065), age difference was significant between older HIV^- and HIV^+ patients ($P \leq 0.0001$).

Antiretroviral therapy

Preferred drugs included raltegravir and dolutegravir for the INSTI class, maraviroc for CCR5 receptor antagonist, lamivudine for NRTI, and rilpivirine for NNRTI.

These antiviral drugs were largely used in our Center as they offered the advantage of having no drug interactions and minimal toxicity. Indeed, 94.7% of patients were on raltegravir or dolutegravir, 66.6% on lamivudine, and 42.1% on maraviroc or rilpivirine, at the end of follow-up (Table 3).

On the other hand, some drugs were avoided when possible: these included boosted regimens and some NNRTIs (risk of pharmacological interactions), tenofovir disoproxil fumarate (risk of renal toxicity), and abacavir (apparent risk of cardiovascular disease).

Patient and graft survival. Patient survival among all HIV^+ recipients at one, three, and five years was 94.4%, 94.4%, and 70.8%, respectively. One-, three-, and five-year graft survival rates were 84%, 72%, and 55.6%, respectively. Graft survival censored for patient death at one, three, and five years was 94.7%, 81.4%, and 81.7%, respectively (Table 4).

Delayed graft function occurred in 17% (n = 3) of KT recipients. Three patients died with a functioning graft from cardiovascular causes. Four patients had graft failure due to AMR (n = 2) and allograft nephrectomy (n = 2). Only two patients with persistent and untreated HCV replication had a poor outcome: one resumed hemodialysis one year after transplantation owing to complications of severe infectious disease (suppurative bacterial pyelonephritis caused by

Table 2. Immunosuppressive agents used during follow-up in HIV^+ KT recipients.

	Month 1	Month 3	Month 6	Month 12	Month 36	Month 60
Patient, n	18	17	17	17	8	5
Cys (C0/C2) + EVL						
n (%)	8 (44%)	7 (41%)	7 (41%)	7 (41%)	4 (50%)	2 (40%)
Mean trough level (ng/mL)	116/503 +7.5	124/551 + 6.9	77/420 + 7.6	71/377 + 6.3	46/263 + 4.7	62/205 + 5.7
TAC						
n (%)	9 (50%)	9 (53%)	9 (53%)	6 (35%)	–	–
Mean trough level (ng/mL)	8.9	7.6	6.3	6.1		
SIR						
n (%)	–	–	–	3 (18%)	1 (12%)	1 (20%)
Mean trough level (ng/mL)				7.75	6.1	6.1
Cys (C0/C2)						
n (%)	1 (6%)	1 (6%)	1 (6%)	1 (6%)	3 (38%)	2 (40%)
Mean trough level (ng/mL)	215/1286	80/542	45/549	121/597	144/557	148/395
MPA						
n (%)	–	1 (6%)	2 (12%)	3 (18%)	–	–
Mean dose (mg/day)		1080	720	600		
Steroid[a]						
n (%)	18 (100%)	15 (88%)	14 (82%)	12 (71%)	4 (50%)	1 (20%)
Mean dose (mg/day)	13.1	7.9	5.4	6.3	2.75	2

Cys: cyclosporine; C0/C2: cyclosporine trough (C0) and 2-h postdose (C2); TAC: tacrolimus; SIR: sirolimus; EVL: everolimus; MPA: mycophenolic acid.
[a]Methylprednisolone.

Table 3. Combination highly active antiretroviral therapy (HAART) at pre-transplantation, early post-transplantation, and last HAART.

Patient	Pre-transplantation HAART			Early Post-Transplantation HAART			Last HAART		
1	Raltegravir	Atazanavir	Lamivudine	Raltegravir	Rilpivirine	Lamivudine	Raltegravir	Rilpivirine	Lamivudine
2	Raltegravir	Abacavir	Lamivudine	Raltegravir	Rilpivirine		Raltegravir	Rilpivirine	
3	Enfuvirtide	Abacavir	Lamivudine	Raltegravir	Rilpivirine	Maraviroc	Raltegravir	Rilpivirine	Maraviroc
4	Raltegravir	Maraviroc	Lamivudine	Raltegravir	Maraviroc	Lamivudine	Raltegravir	Maraviroc	Lamivudine
5	Raltegravir	Rilpivirine	Maraviroc	Raltegravir	Abacavir	Maraviroc	Raltegravir	Rilpivirine	Lamivudine
6	Raltegravir	Lopinavir/ritonavir		Raltegravir	Abacavir	Lamivudine	Raltegravir	Abacavir	Lamivudine
7	Dolutegravir	Rilpivirine	Maraviroc	Dolutegravir	Rilpivirine	Maraviroc	Dolutegravir	Rilpivirine	Maraviroc
8[a]	Raltegravir	Darunavir/ritonavir	Tenofovir[b]	Raltegravir	Darunavir/Ritonavir		Raltegravir	Emtricitabina	Tenofovir[c]
9	Raltegravir	Darunavir/ritonavir	Etravirine	Raltegravir	Etravirine	Darunavir	Dolutegravir	Rilpivirine	Maraviroc
10	Tenofovir	Indinavir/ritonavir	Lamivudine	Raltegravir	Lamivudine	Maraviroc	Raltegravir	Lamivudine	Maraviroc
11	Raltegravir	Darunavir/ritonavir		Raltegravir	Abacavir	Lamivudine	Raltegravir	Lamivudine	Maraviroc
12	Emtricitabine	Darunavir/ritonavir	Tenofovir[b]	Darunavir	Lamivudine	Maraviroc	Darunavir	Lamivudine	Maraviroc
13	Atazanavir	Abacavir		Enfuvirtide	Tenofovir	Lamivudine	Raltegravir	Atazanavir	Lamivudine
14	Saquinavir	Abacavir	Lamivudine	Enfuvirtide	Abacavir	Lamivudine	Dolutegravir	Rilpivirine	Lamivudine
15	Enfuvirtide	Tenofovir[b]	Lamivudine	Raltegravir	Lamivudine		Raltegravir	Maraviroc	
16	Atazanavir	Tenofovir[b]	Lamivudine	Raltegravir	Enfuvirtide	Lamivudine	Raltegravir	Atazanavir	Lamivudine
17	Tenofovir[b]	Atazanavir/Ritonavir	Lamivudine	Raltegravir	Abacavir	Lamivudine	Raltegravir	Atazanavir	Lamivudine
18	Abacavir	Fosamprenavir/ritonavir		Raltegravir	Fosamprenavir	Lamivudine	Raltegravir	Atazanavir	Lamivudine
19	Tenofovir[b]	Atazanavir/Ritonavir	Lamivudine	Raltegravir	Enfuvirtide	Lamivudine	Dolutegravir	Rilpivirine	

The order of the listed patients does not reflect the order of transplantation.
[a]Patient with hepatitis B virus (HBV) infection
[b]Tenofovir disoproxil fumarate.
[c]Tenofovir alafenamide.

Table 4. Survival rates by HIV status and additional patient characteristics.

		Patient survival (%)			Graft survival (%)			Death-censored graft survival (%)		
Recipient	n	1 year	3 years	5 years	1 year	3 years	5 years	1 year	3 years	5 years
HIV+	19	94.4	94.4	70.8[a]	89.5	77.1	57.8	94.7	81.4	81.7
HIV^{-}[b]	200	98.9	95.6	92.9[c]	91.4	82.1	78.3	92.4	85.9	84.3
HIV^{-} aged $\geq$ 65 years[b]	33	96.6	88.5	69.5	84.8	66.1	48.7	87.7	74.7	70.0

[a]Statistically significant difference between HIV^{+} recipients and all HIV^{-} recipients.
[b]Single kidney transplantation from deceased donor from January 2008 to September 2016.
[c]Statistically significant difference between HIV^{-} recipients and HIV^{-} recipients aged $\geq$65 years.

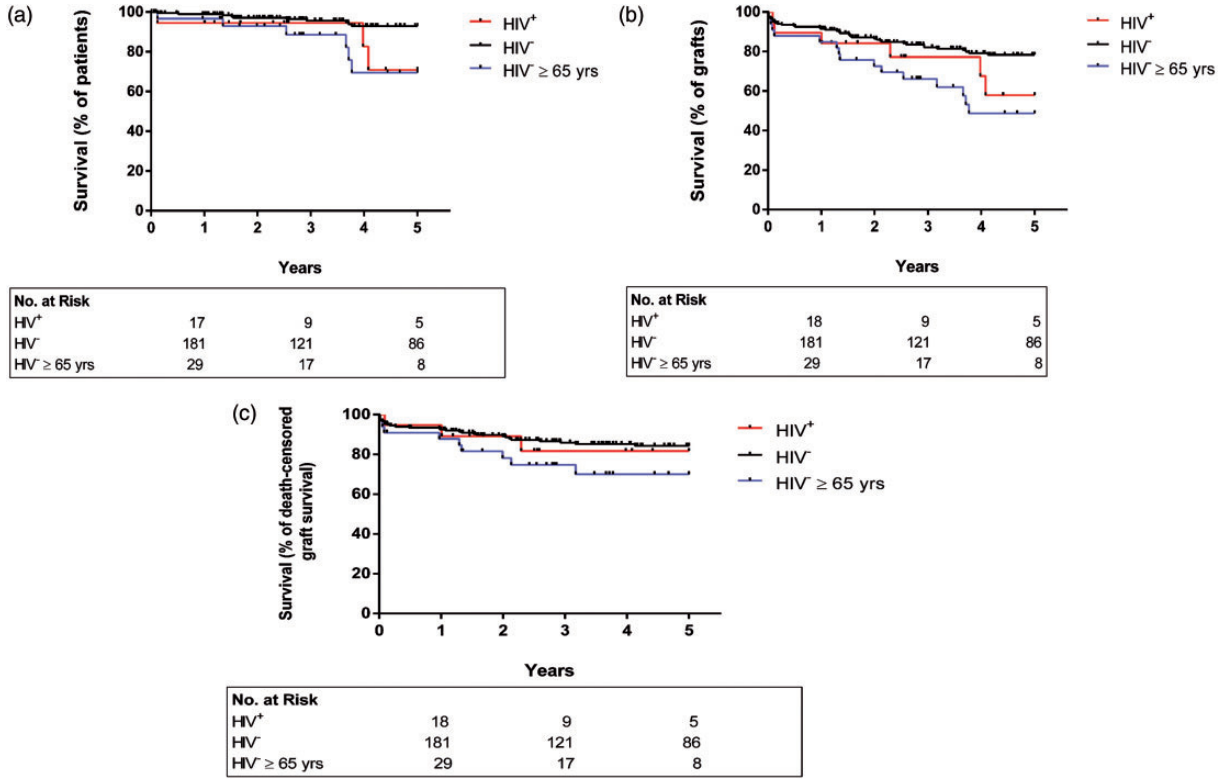

Figure 1. Kaplan–Meier survival curves. Kaplan–Meier estimates of patient (a), graft (b), and death-censored graft survival (c) in HIV^{+} and HIV^{-} patients who underwent kidney transplantation at our Center during the same time frame. Uninfected kidney transplant recipients were stratified by age in two groups: older recipients (aged $\geq$ 65 years) and all recipients. HIV^{+} kidney transplant recipients had a significantly inferior five-year patient survival rates compared to HIV^{-} kidney-transplant recipients (P = 0.03) and a similar rate (P = 0.79) compared to older recipients. Five-year graft survival rates of HIV^{+} recipients were between those reported for older kidney transplant recipients and for all kidney transplant recipients; there were no significant differences between HIV^{+} and all HIV^{-} recipients (P = 0.14) and HIV^{+} and older HIV^{-} recipients (P = 0.44). Death-censored graft survival rates at five years between HIV^{+} and all HIV^{-} recipients (P = 0.72) and HIV^{+} and older HIV^{-} recipients (P = 0.54) were not statistically significant.

atypical mycobacteria), and one died of a sudden acute myocardial infarction four years from transplantation.

Patient, graft, and death-censored graft survival among all HIV^{-} recipients and HIV^{-} recipients aged $\geq$65 years at one, three, and five years are illustrated in Table 4 and Figure 1.

Compared with all HIV^{-} recipients, HIV^{+} had similar one-year (94.4% vs. 98.9%, P = 0.12) and three-year (94.4% vs. 95.6%, P= 0.6) patient survival and

similar one-year (89.5% vs. 91.4%, P = 0.76) and three-year (77.1% vs. 82.1%, P = 0.53) graft survival.

Kaplan–Meier analysis showed that HIV^+ patients compared to all HIV^- had a significantly inferior patient survival rate (70.8% vs. 92.9%, P = 0.03) and a non-statistically significant lower graft survival (57.8% vs. 78.3%, P = 0.14) at five years (Table 4 and Figure 1(a) and (b)).

In contrast, HIV^+ recipients, compared to HIV^- recipients aged ≥65 years, had a similar survival rate (70.8% vs. 69.5%, P = 0.794) and non-statistically significant higher graft survival rate at five years (57.8% vs. 48.7%, P = 0.44) (Table 4 and Figure 1(a) and (b)). When death-censored graft survival rates at five years were evaluated, HIV^+ recipients had a similar survival rate compared to all HIV^- recipients (81.7% vs. 84.3%, P= 0.72), and non-statistically significant higher survival rates compared to HIV^- KT patients older than 65 years (81.7% vs. 70%, P= 0.54) (Table 4 and Figure 1(c)).

Allograft rejection. Nine patients (47.4%) had 14 allograft rejections during the follow-up (Table 5). There were eight TCMR episodes (57%), four AMR episodes (29%), one mixed rejection episode (7%), and one chronic AMR (7%). Half of the episodes of rejection occurred during the first six months after transplantation and were mostly TCMR. After one year from transplantation, AMR was the most common type of rejection. All cases of acute T-cell rejection were responsive to high-dose corticosteroids. Acute AMR occurred in four KT recipients (two women and two men) after a median age of 1.1 years from transplantation. Three patients resumed hemodialysis whereas one patient had severe renal impairment (stage 4 vs. stage 1 of chronic kidney disease) at the end of the follow-up. The cumulative incidence of rejection at one, three, and five years was 32.9%, 40.3%, and 48.8%, respectively. Patients treated with Cys/EVL had a higher one-year cumulative acute rejection rate than patients treated with TAC (50% vs. 33.3%) within the first year, but this difference was not statistically significant (P= 0.64).

Table 5. Renal outcome of HIV^+ kidney transplant recipients (n = 19).

Median eGFR[a] (IQR), mL/min/1.13m^2	
Month 3	70 (48–82)
Month 6	66 (42–78)
Month 12	41 (33–708)
Month 36	53 (36–74)
Month 60	56 (54–58)
Type of rejection (n=14)	
T-cell-mediated	57% (n=8)
Antibody-mediated	29% (n=4)
Mixed	7% (n=1)
Chronic antibody-mediated	7% (n=1)
Episodes of rejection	
≤6 months	
T-cell-mediated	6
Antibody-mediated	1
6–12 months	
T-cell-mediated	1
Mixed	1
>12 months	
T-cell-mediated	1
Antibody-mediated	3
Chronic antibody-mediated	1

Mixed denotes mixed cellular and antibody-mediated rejection.
[a]eGFR, estimated glomerular filtration rate using the CKD-EPI formula.

Progression of HIV disease. All patients were on HAART before they underwent kidney transplantation; they had an undetectable VL, a median CD4+ T-cell count of 407 cells/mm^3 (IQR, 367–556), and CD4/CD8 ratio of 0.64 (IQR, 0.46–0.96) at time of kidney transplantation.

The change in the CD4+ T-cell count from baseline at one, three, and five years after transplantation were 478 (IQR, 414–630), 449 (IQR, 353–714), and 659 (365–791) cells/mm^3, respectively. In 18 patients, plasma HIV-RNA was undetectable at any time after transplantation. Only one patient had a detectable viremia six years after transplantation that was unresponsive to change in several ART regimens; conversion to sirolimus (SIR) (target TTL of 5–7 ng/ml) from Cys and EVL was required to control the rate of viral replication.

Complication after kidney transplantation. Among 19 kidney transplant recipients, 10 patients (72%) experienced 25 episodes of infections during the follow-up; hospital admission was required only in 11 cases. Infections were caused by bacteria (46%) and fungi (36%); cultures were negative for the remaining 18%. The site of infection was lung (55%), genitourinary (36%), and central nervous system (9%). About 70% of the infections occurred within the first two years after transplantation.

Three cases of *Pneumocystis jirovecii* pneumonia were diagnosed in two subjects with CD4+ T-cell count higher than 200 cells/mm^3. HHV8 viremia was identified in three patients but only one developed a Kaposi sarcoma. CMV replication was detected after specific prophylactic therapy in 2 out of in 15 patients tested (13%), and only one required specific antiviral treatment. CMV infection was susceptible to ganciclovir and was treated successfully with valganciclovir. Detection of EBV replication was found in 15 of 17 patients tested; five patients had a persistent viremia

from the early post-transplant period to the end of follow-up. The median EBV-VL was 362 copies/ml (IQR, 75–2427). Despite the high prevalence of EBV replication, no patient developed EBV-related post-transplant lymphoproliferative disease. Of the 17 patients who were tested for polyomavirus BK and JC virus, peripheral blood viremia was detected in 47% and 18% of patients, respectively. There was one case of biopsy-proven BK nephropathy.

De novo endocrine and metabolic complications developed in 14 subjects (68%) after kidney transplantation, including diabetes (43%), hypercholesterolemia (36%), sarcopenia (29%), cardiovascular events (21%), hypothyroidism (14%), osteopenia (14%), and osteoporosis (7%).

Other complications were two cases of avascular necrosis of the femoral head, and one case each of deep venous thrombosis, acute pancreatitis, and demyelinating polyneuropathy.

Two patients (11%) underwent graft nephrectomy: one due to interstitial hemorrhage secondary to acute AMR rejection and one for suppurative bacterial pyelonephritis.

Neoplasm. One case of neoplasm was reported. The tumor was a cutaneous Kaposi sarcoma involving the skin, diagnosed after 0.9 years from kidney transplantation. Complete tumor resolution was achieved after two months from diagnosis with withdrawal of immunosuppressive therapy due to graft failure.

Discussion

After the first recognition in 2003 that kidney transplantation was a safe and effective solution for HIV-infected patients reaching ESRD,[17] HIV infection was no longer considered an absolute contraindication to transplantation. Although prospective[12,17,18] and retrospective studies[13,19] have reported promising results, HIV-associated comorbidities, high prevalence of acute allograft rejections, and the lack of consensus guidelines for the management of immunosuppression have the potential to negatively affect long-term outcomes of transplantation in HIV^+ patients. With the present study, we report clinical outcomes of 19 HIV^+ subjects who underwent kidney transplantation from deceased donors. The study, conducted among patients with a median age of 50 years and mainly of Caucasian origin, showed excellent graft and patient survival rates at one year and three years. These data were highly comparable with those observed in HIV^- KT recipients transplanted at our center during the same time frame. When we extended analysis out to five years, we found a significantly lower patient survival rate (70.8% vs. 92.9%, P= 0.03) and a non-significant trend toward reduced rates of graft survival (57.8% vs. 78.3%, P= 0.14) compared with the general pool of HIV^- recipients.

Interestingly, the difference between graft survival rates became less evident when data were censored for death (81.7% vs. 84.3%, P = 0.72), indicating a substantial impact of mortality on long-term graft outcome in HIV^+ patients.

Overall, HIV^+ recipients had survival rates generally between rates found in all HIV-uninfected recipients and recipients older than 65 years, a tendency already noted by Stock et al.[12] in a larger population of HIV^+ KT recipients. These findings suggested that HIV^+ recipients had an higher risk of death than uninfected controls of the same age. We hypothesize that T-cell senescence, advanced atherosclerosis, and non-AIDS-related disorders may be the leading causes of exitus in this group of subjects. First, patients with HIV may have T-cell dysfunction[20] similar to older patients that contributes to the increased incidence of morbidity and mortality from infectious disease, and possibly autoimmunity and cancer.[21] Second, both age and HIV infection[22] lead to increased likelihood of developing atherosclerosis and small vessel disease which generally predisposes to coronary and cerebrovascular events. Finally it is well-known that, in the HAART era, non-AIDS-related disorders, such as cardiovascular disease, cancer, and liver disease, are the major causes of morbidity and mortality among these patients.[23,24] We believe that despite careful patient selection, the first patients who were enrolled for kidney transplantation could have had a potentially poorer outcome compared to both actual HIV^+ patients and non-infected counterparts. Probable causes may have been inadequate management of HIV disease during the late 1980s and 1990s, when control of VL was particularly challenging and delay in diagnosis, linkage to care, and treatment were particularly common.

A major concern in our study was the high frequency of episodes of allograft rejections that have been associated with a 2.8-fold greater risk of graft loss in the setting of HIV infection.[12] In line with the current literature that estimates the one-year cumulative incidence of acute rejection up to 52%,[12,25] we detected a rate of 32.9% in our HIV^+ population. The episodes of rejection, developed mainly during the first six months after transplantation, were mostly T-cell mediated and responsive to glucocorticoid. Beyond one year from transplantation, AMR became prevalent. The treatments of rejection were well tolerated, without the development of opportunistic infections or any significant drop in CD4+ T-cell count.

The causes of the increased risk of rejection in HIV^+ KT patients are still unclear. Stock et al.[12] proposed

that several mechanisms related to the chronic HIV infection may be responsible for an excessive allogeneic response against graft antigens; in fact, HIV is able to incorporate HLA molecules of the host into its genome that may induce allosensitisation and is able to increase the responsiveness of T-lymphocyte and stimulation of memory alloreactive T lymphocyte due to cross-reactivity. In light of our results, we presume that our past tendency to minimize immunosuppression, in order reduce the risk of infection, could have contributed to the high rates of rejection in this cohort of patients. According to this hypothesis, both Gruber et al.[26] and Touzot et al.[13] reported low rejection rates at one year (13 and 15%, respectively) in patients treated with anti-IL-2 for induction and a standard triple calcineurin inhibitor-based immunosuppression for maintenance, without documenting a high incidence of opportunistic infections. Given that, there is a growing awareness that HIV^+ KT recipients should receive the same amount of immunosuppressive therapy as HIV^- patients, our past strategy aiming at maintaining HIV^+ KT recipients on low-grade immunosuppression (EVE with low-dose Cys and steroid) has been definitely abandoned. On the basis of these observations, we enhanced immunosuppressive therapy using a standard protocol based on TAC, MPA, and steroid. TAC was preferred to Cys because was superior in preventing rejection as demonstrated also in HIV^+ KT recipients.[27]

Infections have been reported as common complications of kidney transplantation. In our group of HIV^+ KT recipients, infections were mainly bacterial and resolved with appropriate antibiotic therapy. *Pneumocystis jirovecii* pneumonia occurred three times in two patients after more than two years from transplantation; a CD4+ T-cell count $\geq$200 cells/mm^3 at the time of the event suggests that these infections were a complication of the immunosuppressive therapy rather than AIDS-defining illnesses.[28]

Surprisingly, the rate of CMV replication was exceptionally low in our HIV^+ patients; only one subject required specific therapy. The low rates of CMV viremia were probably due to the high rate of CMV seroprevalence among recipients (95%), and the efficacy of extended valganciclovir prophylaxis after kidney transplantation.[29,30] We underline that prolonged duration of CMV prophylaxis (12 months) was dictated by the institutional protocol and not by the current recommendations in HIV^+ KT recipients. Given that CMV infection does not seem particularly prevalent in this population, the standard approach is to perform CMV prophylaxis similar to HIV^- KT recipients.

Overall, HIV-infected KT recipients did not display an increased susceptibility to opportunistic and non-opportunistic infections. The ability to mount an efficacious immune response, as evidenced by the high rate of allograft rejections, apparently indicates a preserved immune response towards pathogens in these subjects. In accordance with the findings of the present report, there was no evidence of an accelerated progression of HIV infection after KT. Only one patient experienced recurrent viraemia poorly controlled by HAART; in this case, the switch of immunosuppression from Cys to SIR reduced the rate of detectable viremia leading to a more stable control of HIV infection.

After transplantation, more than half of our patients developed de novo metabolic complications including diabetes, cardiovascular disease, sarcopenia, and hypercholesterolemia. Main causes of these complications relied on a combination of pre-existing risk factors such as HIV infection,[31] antiretroviral therapy,[32–34] and well-known side effects of immunosuppressive therapy (e.g. steroids, calcineurin inhibitor) post-transplantation.

Our study has several limitations. The main shortcomings include the small number of patients, the short interim follow-up and the retrospective design of the study. Sample size is too small to assess the association of recipient mortality and graft loss with different demographic and clinical variables. We cannot evaluate if HIV^+ KT recipients were exposed to more adverse events compared to their uninfected counterpart because the rates of metabolic complications, allograft rejections, and infections between the two groups have been not compared.

Moreover, it is worth noting that the limited number of subjects ($n = 5$) at the end of the five-year follow-up is inadequate to properly assess long-term graft outcomes; therefore, our results cannot be generalized to all HIV^+ KT recipients. However, this study provides a thorough analysis of long-term follow-up from one of the few cohorts of HIV-infected recipients of kidney transplantation worldwide.

In conclusion, our study presents clinical outcomes of a small series of HIV^+ KT recipients mostly of Caucasian origin. Analysis of patient and graft outcomes confirms an excellent survival at one year and three years post-transplantation. On the other hand, there was a significant tendency toward inferior long-term patient survival, similar to HIV^- recipients aged $\geq$65 years, which influenced graft outcome. We reported a high prevalence of allograft rejection episodes, probably caused by the reduced intensity of immunosuppression provided to HIV^+ patients in order to reduce the risk of HIV-related opportunistic infections, which do not appear to be particularly increased in our cohort. Larger multicenter studies are needed in order to evaluate the best immunosuppressive treatment for HIV^+ KT patients, for the sake

of improving long-term outcomes and reducing the prevalence of metabolic complications.

Author Contributions

GA and GG designed the study; GA and FF wrote the paper; GM, FF, AB, GD, AS, and AF collected data; EF analyzed data; and CM, GG, and GC reviewed the paper.

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