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High incidence of delayed graft function in HIV-infected kidney transplant recipients

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Summary

Kidney transplantation (KT) outcomes in human immunodeficiency virus (HIV)-infected recipients are under continuous research. High incidence of early post-transplant complications such as acute rejection has been observed. A multicenter study including HIV-infected patients who underwent KT in Spain, from 2001 to 2011, was performed. The study population included 108 recipients, 36 HIV-infected, and 72 matched HIV-negative KT recipients. HIV-infected recipients developed more delayed graft function (DGF) (52% vs. 21%, $P < 0.001$). One- and 3-year graft survival was 91.6% and 86.2% in HIV-infected patients, and 97.1% and 94.7% in HIV-negative patients ($P = 0.052$). In two-variate Cox analysis, HIV infection was not a predictor of graft loss after adjusting for time on dialysis, acute rejection, and DGF. Multivariate analysis for DGF revealed HIV-positive status as independent risk factor. We analyzed the evolution of immunosuppressive and antiretroviral therapy (ART). In HIV-infected patients tacrolimus trough levels were very high in the first week and significantly lower in the second week post-transplant ($P = 0.042$). Post-transplant ART was significantly changed: protease inhibitors use decreased ($P = 0.034$) and integrase inhibitor use increased ($P < 0.001$). DGF is another frequent early complication in HIV-infected recipients that can affect graft survival. Strategies to prevent DGF and antiretroviral regimes with less drug interactions could improve outcomes.

Introduction

Human immunodeficiency virus (HIV) infection has ceased to be a contraindication in solid-organ transplant. In the last decade, numerous studies have shown that kidney transplantation (KT) is safe and does not worsen evolution of the HIV infection [1–9]. However, experience is still scarce, especially in Europe [4,6,7].

The Spanish Group for Advancement in Transplantation (GREAT group) includes 21 Spanish hospitals that perform KT. In 2008, we set up a multicenter study to analyze the outcomes of KT in HIV-infected patients compared to HIV-negative KT patients (TRASRENVIH study). We reported a first analysis including HIV-infected KT recipients until 2009, and the current study is its continuation [6].

A higher incidence of acute rejection in the early post-transplant period has been noticed in the largest series of HIV-infected KT recipients, and some studies also describe a high incidence of delayed graft function (DGF) [1–3,6,8,9]. Both factors can affect graft survival [2,3,10,11]. However, the high frequency of DGF has not been previously highlighted. Also, the evolution of immunosuppressive and antiretroviral therapy (ART) is poorly known especially in the first weeks after transplantation. We have focused our analysis on these issues not examined until now and which may affect graft survival.

Patients and methods

This is a multicenter, retrospective cohort study including HIV-infected patients who underwent KT in Spain in the era of the combined ART (cART), from January 2001 to December 2011. Patients who received combined KT with other organs were not included. A control group was selected, including two HIV-negative KT performed at the same hospitals (±12 months), according to the following criteria, with the priority in which they are listed: KT number, donor age (±10 years), recipient age (±10 years), pretransplant peak panel reactive antibodies (PRA), donor type, Hepatitis C virus (HCV)/Hepatitis B virus recipient serostatus, initial immunosuppression, time on dialysis (±5 years), donor and recipient sex. The study was approved by the institutional review boards of the participating centers. All the patients signed an informed consent form.

Patients

The selection of HIV-infected patients for transplant was similar at all centers, following Spanish guidelines recommendations [6,12]. All patients had pretransplant CD4 count >200 cells/mm^3. In patients without criteria to commence cART pretransplant, detectable low-level viremia was admitted, starting cART after KT [12]. In most hospitals, patients continued on the same cART after KT, although subsequent changes were frequent.

Prophylaxis for opportunistic infections was administered according to Spanish guidelines [13] and initial immunosuppressive therapy according to local protocols, both without differences between groups. The main prophylactic therapies for infections included trimethoprim-sulfamethoxazole for Pneumocystis (at least 6 months), ganciclovir/valganciclovir for cytomegalovirus (at least 3 months) and isoniazid for patients with a past history of tuberculosis (9 months). AR episodes were confirmed by biopsy and treated according to local protocols.

Clinical database and variables

The TRASRENVIH database is an online database (SQL Server) in which the data were collected by a transplant physician, with access to the database being protected by a blinded code. Data are transferred to an independent biometry unit and analyzed according to the suggestions provided by the GREAT working group. The database includes variables regarding recipients, donors, and transplant outcomes (listed in Table 1). Serum creatinine levels, glomerular filtration rate (GFR), proteinuria, immunosuppressive doses/trough levels were periodically collected at: week 1, week 2, month 1, month 3, and annually thereafter. Plasma HIV-1 RNA levels, CD4+ T-cell counts, and antiretroviral drugs were collected with the same frequency, and also when opportunistic events were diagnosed.

Delayed graft function was defined as the need for dialysis in the first week after surgery (in absence of other causes) with subsequent recovery of kidney function. Acute rejection was defined according to the Banff classification. Borderline changes in the biopsy were recorded as a rejection episode when the patient received anti-rejection treatment. Diabetes Mellitus was defined in accordance with the American Diabetes Association criteria [14].

Statistical analysis

Variables are presented as means and standard deviation, medians, and interquartile range (IQR), or as frequency, and these were compared using *t*-test, Mann–Whitney U test, chi-square test or Fisher's exact test, as appropriate. McNemar test was used to compare ART before and after KT. Comparison of collected serial variables (GFR, immunosuppressive doses/trough levels) was made using linear mixed-effects models. Patient and graft survival and acute rejection were calculated using the Kaplan–Meier method and groups were compared using the log-rank test. A two-sided P-value < 0.05 was considered statistically significant. Statistical analysis were performed using R version 2.13.0.

Two-variate Cox proportional-hazard models for allograft loss were estimated including HIV status and another covariate. Covariates with recognized influence on graft survival were selected (Table 2). Acute rejection was treated as a time-varying covariate.

Risk factors for DGF were analyzed first in two-variate logistic regression models including HIV status and another covariate. Covariates that have been related in previous reports with DGF development were included: donor and

recipient age, recipient HCV seropositivity, recipient body mass index (BMI), pretransplant diabetes mellitus, time on dialysis, type of dialysis, PRA > 20%, human leukocyte antigen mismatch, donors after cardiac death (DCD), cold ischemia time (CIT), induction therapy, and tacrolimus doses/levels in the first week. Subsequently, all variables from two-variable models with $P < 0.1$ were included in multivariate logistic regression models (Table 3).

Table 1. Characteristics of donors and recipients and post-transplant variables.

	HIV-infected patients ($n = 36$)	HIV-negative patients ($n = 72$)	*P*-value
Recipient age (years)*	44.3 (9.8)	43.3 (9.8)	0.476
Male recipients, *n* (%)	27 (75)	48 (67)	0.375
Caucasian recipients, *n* (%)	33 (92)	70 (97)	0.107
BMI (kg/m^2)*	22.6 (3.5)	25.1 (3.9)	0.002
Cause of renal failure, *n* (%)			0.651
Glomerulonephritis	12 (33)	18 (25)	
Diabetes	3 (8)	8 (11)	
HIVAN	1 (3)	–	
Unknown	9 (25)	13 (18)	
Other	11 (31)	33 (46)	
Duration of pre-transplant dialysis (months)†	49.5 (29–84)	25 (15–38)	<0.001
Peritoneal dialysis, *n* (%)	8 (22)	22 (30)	0.182
PRA > 20%, *n* (%)	1 (3)	7 (10)	0.391
HBV-positive recipients, *n* (%)	2 (5)	0	0.207
HCV-positive recipients, *n* (%)	15 (42)	11 (15)	0.005
CMV IgG-positive recipients, *n* (%)	30 (83)	51 (72)	0.283
Pretransplant opportunistic infections, *n* (%)	19 (53)	7 (10)	<0.001
Bacterial infection	16 (44)	7 (10)	
Fungal infection	1 (3)	0	
Protozoan infection	3 (8)	0	
Viral infection	5 (14)	0	
Donor age (years)*	45.7 (13.6)	46.3 (14.0)	0.836
Male donors, *n* (%)	24 (67)	44 (61)	0.724
Donor type, *n* (%)			0.117
Deceased-brain death	31 (86)	65 (90)	
Deceased-cardiac death	3 (8)	2 (3)	
Living donor	2 (6)	5 (7)	
Cause of donor brain death, *n* (%)			0.734
Vascular	18 (58)	45 (69)	
Cranial trauma	8 (26)	13 (20)	
Other	5 (16)	7 (11)	
HCV-positive donor, *n* (%)	2 (5)	1 (1)	0.534
CMV IgG-positive donors, *n* (%)	26 (72)	50 (69)	0.488
Previous transplant, *n* (%)	2 (5)	4 (5)	0.656
HLA mismatches (DR+B+A)*	3.9 (1.3)	3.7 (1.1)	0.137
Cold ischemia time (h)*	15.5 (5.7)	14.5 (6.2)	0.417
Initial immunosupression, *n* (%)			0.530
Steroids	36 (100)	72 (100)	
Tacrolimus	34 (94)	67 (93)	
Mycophenolic acid	36 (100)	71 (99)	
Cyclosporin	2 (6)	4 (6)	
Sirolimus	0	1 (1)	
Anti-IL2R/Thymoglobulin induction	11 (30)/4 (11)	20 (28)/6 (8)	
DGF, *n* (%)	19 (52)	15 (21)	<0.001
DGF (excluding DCD), *n* (%)	16 (44)	13 (18)	0.001
Pathologic rejection diagnosis, *n* (%)			0.025
Borderline/IA	3 (30)/0 (0)	2 (18)/7 (78)	
IB	1 (15)	1 (11)	
IIA	4 (57)	1 (11)	
Antibody-mediated	2 (28)	0	

Table 1. continued

	HIV-infected patients (n = 36)	HIV-negative patients (n = 72)	P-value
GFR (MDRD-4)†,‡			–
1st week	12 (7–25) [n = 35]	33 (12–55) [n = 69]	
2nd week	24 (11–38) [n = 34]	39 (26–59) [n = 68]	
1st month	44 (28–57) [n = 32]	47 (39–59) [n = 68]	
3rd month	52 (42–65) [n = 32]	54 (41–65) [n = 68]	
1st year	59 (51–70) [n = 24]	54 (44–71) [n = 56]	
3rd year	55 (44–61) [n = 12]	53 (39–69) [n = 37]	
Post-transplant opportunistic infections, n (%)	16 (45)	38 (53)	0.622
Bacterial infection	41 (84)	54 (72)	
Fungal infection	2 (4)	2 (3)	
Viral infection	6 (12)	19 (25)	
Sites of bacterial infection, n (%)			0.043
Genitourinary tract	19 (47)	39 (72)	
Respiratory tract	12 (29)	4 (7)	
Other	10 (24)	11 (21)	
Post-transplant malignancies, n (%)	4 (11)	3 (4)	0.272
Skin carcinoma	3	2	
Kaposi's sarcoma	1	0	
Breast carcinoma	0	1	
Lymphoproliferative disorder	1	0	

*Mean and standard deviation.
†Median and interquartile range.
‡The comparison of GFR data was made using linear mixed-effects model. In HIV-infected recipients, GFR was lower in the early post-transplant period (value = −10.17; P = 0.021). Then, the slope of change over time was significantly greater (value = 0.56; P = 0.016) equaling the GFR in both groups.
BMI, body mass index; DCD, donor after cardiac death; DGF, delayed graft function; HIVAN, HIV-associated nephropathy; PRA, panel reactive antibodies; HBV, hepatitis B virus; HCV, hepatitis C virus; CMV, cytomegalovirus; HLA, human leukocyte antigen; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease.

Table 2. Two-variate Cox proportional-hazard models for allograft loss.

	HIV status		Covariate	
Model	HR (95% CI)	P-value	HR (95% CI)	P-value
HIV + DGF	2.06 (0.43–9.74)	0.366	4.22 (0.77–21.04)	0.090
HIV + Acute rejection*	2.84 (0.79–10.23)	0.110	3.12 (0.70–13.7)	0.135
HIV + Time on dialysis	2.92 (0.74–11.569	0.129	1.08 (0.58–2.01)	0.803
HIV + Pre-transplant Diabetes	3.22 (0.90–11.44)	0.074	1.58 (0.33–7.59)	0.566
HIV + Recipient age	3.27 (0.92–11.60)	0.069	1.04 (0.97-1-11)	0.256
HIV + Donor age	3.24 (0.91–11.48)	0.072	1.02 (0.97–1.07)	0.491
HIV + HCV recipient status†	3.00 (0.83–10.88)	0.096	1.74 (0.48–6.32)	0.399
HIV + Induction Therapy‡	3.32 (0.93–11.82)	0.066	1.62 (0.43–6.06)	0.472
HIV + HLA mismatch ≥5	3.26 (0.92–11.57)	0.070	1.19 (0.31–4.62)	0.798

*First acute rejection episode.
†HCV-positive recipient status.
‡AntiCD25 induction and/or thymoglobulin induction.
HR (95% CI), hazard ratio (95% confidence interval); HIV, human immunodeficiency virus; DGF, delayed graft function; HCV, hepatitis C virus; HLA, human leukocyte antigen.

Results

Human immunodeficiency virus-infected patients received KT at 13 hospitals during the study period. During that time, 10283 KT were performed, of which 36 were performed on HIV-infected patients (0.3%). These 36 HIV-infected patients and 72 HIV-negative controls were enrolled. Median follow-up was 33.6 months (IQR, 12.9–59.5) in the HIV group and 37.1 months (IQR, 14–62) in the control group (P = 0.904).

Table 3. Results of the multivariate logistic regression analysis for delayed graft function.

Variable	Odds ratio (95% confidence interval)	*P*-value
HIV-positive recipient status	5.02 (1.48–17.03)	0.009
HCV-positive recipient status	6.56 (2.02–26.23)	0.002
Cold ischemia time	1.13 (1.01–1.25)	0.026
Recipient age	1.10 (1.01–1.20)	0.030
Induction therapy	2.95 (0.94–9.18)	0.062
Recipient body mass index	1.14 (0.98–1.33)	0.089
Donor age	0.96 (0.91–1.01)	0.139

HIV, human immunodeficiency virus; HCV, hepatitis C virus.

Comparison of recipient, donor, and surgery characteristics are shown in Table 1. HIV-infected recipients had a significantly lower BMI and nearly twice the time on dialysis. In Spain, patients with end-stage renal disease have a very low prevalence of HCV infection, so it was not possible to find sufficient control patients with that condition. On the contrary, as in the general population of Spanish HIV-infected patients, HIV–HCV co-infection is highly prevalent [12]. The incidence of pretransplant opportunistic infections was also significantly higher among HIV-infected patients.

Patient and graft survival

There were no significant differences in patient survival between the two groups ($P = 0.285$) (Fig. 1a). All deaths occurred beyond the third year after KT. Two HIV-negative patients died: one because of breast carcinoma (38 months post-transplant), one because of HCV cirrhosis (60 months post-transplant). Three patients in the HIV group died: one because of ischemic stroke (58 months post-transplant), one because of sepsis secondary to pulmonary infection (66 months post-transplant), and one because of Epstein-Barr virus-related B-cell gastrointestinal lymphoma (85 months post-transplant).

One- and 3-year death-censored graft survival was 91.6% (95% confidence interval, CI, 76.1–97.2) and 86.2% (95% CI, 65.6–94.9) in HIV-infected recipients, and 97.1% (95% CI, 89.2–99.2) and 94.7% (95% CI, 83.9–98.3) in HIV-negative recipients, with an almost significant difference ($P = 0.052$) (Fig. 1b). Four HIV-negative patients lost their grafts because of chronic allograft nephropathy (2 grafts) and vascular thrombosis (2 grafts). Seven grafts failed in HIV-infected patients because of chronic allograft nephropathy (4 grafts), vascular thrombosis (2 grafts), and antibody-mediated acute rejection (1 graft).

Two-variate Cox proportional-hazard models for allograft loss are presented in Table 2. HIV infection remained on the borderline of statistical significance ($P < 0.1$) with all covariates, except for time on dialysis, acute rejection, and DGF. Additionally, in the adjusted model for DGF, HIV status was not a predictor of allograft loss while DGF maintained borderline significance (P for DGF = 0.090).

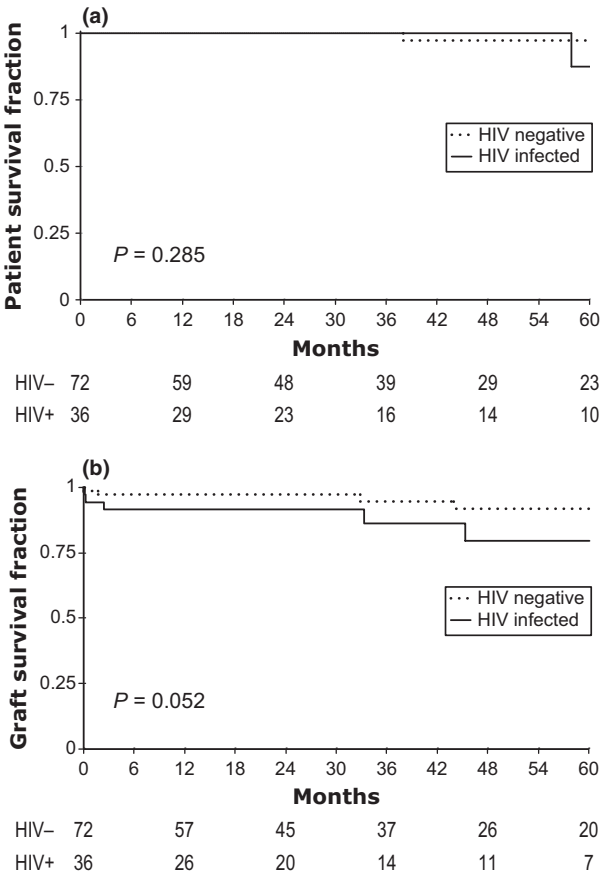

Figure 1 Probability of patient and graft survival in human immunodeficiency virus (HIV)-infected and HIV-negative kidney transplant recipients.

Complications related to renal allograft and immunosuppressive therapy management

Major events after KT are summarized in Table 1.

DGF was very frequent among HIV-infected recipients. Table 3 shows the variables that yielded a P-value < 0.1 in two-variate logistic regression models for DGF. HIV status, recipient HCV status, recipient age, and CIT remained independent predictors of DGF in the multivariate analysis. The whole analysis was repeated excluding recipients with allografts from DCD and from living donors in both groups, with similar results (data not shown).

The probability of a first acute rejection episode was higher among HIV-infected recipients, although without statistical significance: in HIV-infected, 23.8% (95% CI = 12.6–42.1) at 1 year, 33.9% (95% CI = 19.3–55.2) at 3 years; in HIV-negative, 17.4% (95% CI = 10.3–28.7) at

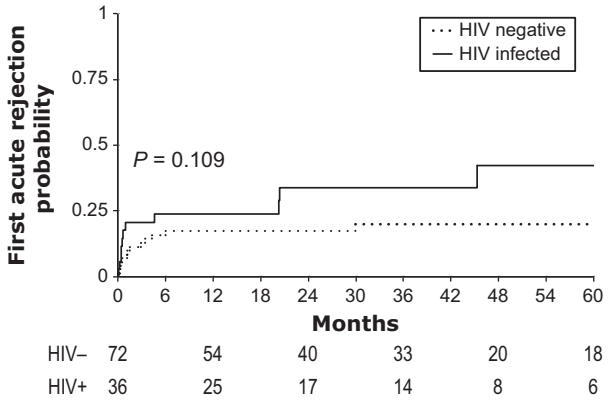

Figure 2 Probability of a first acute rejection episode in kidney transplant recipients according to human immunodeficiency virus (HIV) status.

1 year, and 20% (95% CI = 11.9–32.4) at 3 years ($P = 0.109$) (Fig. 2). The lesions found in biopsies were more severe among HIV-infected patients ($P = 0.025$).

Glomerular filtration rate (GFR) was significantly lower in HIV-infected patients in the first day post-transplant, in relation to the greater incidence of early graft dysfunction ($P = 0.021$). Thereafter, we did not observe differences in renal function in medium term.

Figure 3 shows the evolution of immunosuppressive treatment after KT. Tacrolimus trough levels showed differences especially during the first month post-transplant (Fig. 3b). In HIV-infected recipients, tacrolimus trough levels were higher in the first week, although without significant differences, while they were significantly lower in the second week. The median tacrolimus trough levels in HIV-infected recipients with and without protease inhibitors in the early post-KT period were: 24.5 vs. 9.6 ng/ml in the first week ($P = 0.164$; $n = 9$ vs. 22); 15.2 vs. 7.6 ng/ml in the second week ($P = 0.097$; $n = 4$ vs. 24). The median tacrolimus trough levels in recipients with and without raltegravir were: 9.6 vs. 10.35 ng/ml in the first week ($P = 0.817$; $n = 6$ vs. 25); 7.8 vs. 7.9 ng/ml in the second week ($P = 0.856$; $n = 9$ vs. 30).

As to mycophenolic acid (MPA), we observed a significant drop in the doses received by HIV-infected patients from the first month post-transplant (Fig. 3d). Only half the centers provided MPA trough levels, showing a parallel course to that observed with the doses (data not shown).

HIV disease and ART management after KT

The median CD4+ T-cell count at KT was 420 cells/mm^3 (IQR, 342–546). After KT, median CD4+ T-cell counts remained stable: 413 cells/mm^3 (IQR, 310–728), 497 cells/mm^3 (IQR, 379–612), 570 cells/mm^3 (IQR, 515–714), 627 cells/mm^3 (IQR, 473–788), 618 cells/mm^3 (IQR, 420–639), at 1 month, 3 months, 1 year, 2 years, and 3 years, respectively. Four patients had detectable pretransplant plasma HIV RNA with levels under 2000 copies/mL. At the last visit after KT, only one patient had detectable viremia (152 copies/mL with CD4 count of 1067 cells/mm^3), being the only patient who refused post-transplant ART.

Post-transplant ART evolution (main 4 antiretroviral drug groups) was examined comparing the percentage of patients receiving treatment before transplantation, at any visit post-transplantation, and at the final follow-up visit (Fig. 4). Nucleoside/nucleotide reverse transcriptase inhibitors use remained highly stable. We observed a trend to increase non-nucleoside reverse transcriptase inhibitors use, although without significant differences at the end of the study. Protease inhibitors continued to be administered after KT, but their use dropped significantly at the end. On the contrary, the use of integrase inhibitor (raltegravir) increased most significantly after KT, and that increase was maintained at the end of the study, suggesting a good tolerance to the drug.

Other post-transplant complications

We found no significant differences in the incidence of infections. However, we observed differences in the sites of infection, especially in bacterial infections. As is usual in KT, the incidence of infections of genitourinary tract was very high in HIV-negative recipients, while in HIV-infected recipients, although such infections were also frequent, respiratory infections were equally remarkable. No cases of tuberculosis, other nontuberculous mycobacterial infections or Pneumocystis infections were observed. One HIV-infected patient developed BK polyomavirus nephropathy that was controlled after decreasing the immunosuppressive therapy. A case of Kaposi sarcoma, in an HIV-infected recipient, reverted after changing to a sirolimus-based immunosuppression.

Discussion

The outcomes of KT in our country were similar with those reported in American studies [1–3,8,9]. Our results show that graft survival in HIV-infected patients was lower than that observed in HIV-negative recipients of a similar age and transplant number with a nearly significant difference. Similar to other previously reported series, in our study population, time on dialysis was longer for HIV-infected recipients [1–4]. Likewise, other studies also found, like us, a high incidence of acute rejection and DGF [1–3,8,9]. Multiple explanations for this higher rejection incidence have been reported, such as innate immune system dysregulation, continuous inflammatory state and inadequate exposure to immunosuppressive agents secondary to drug

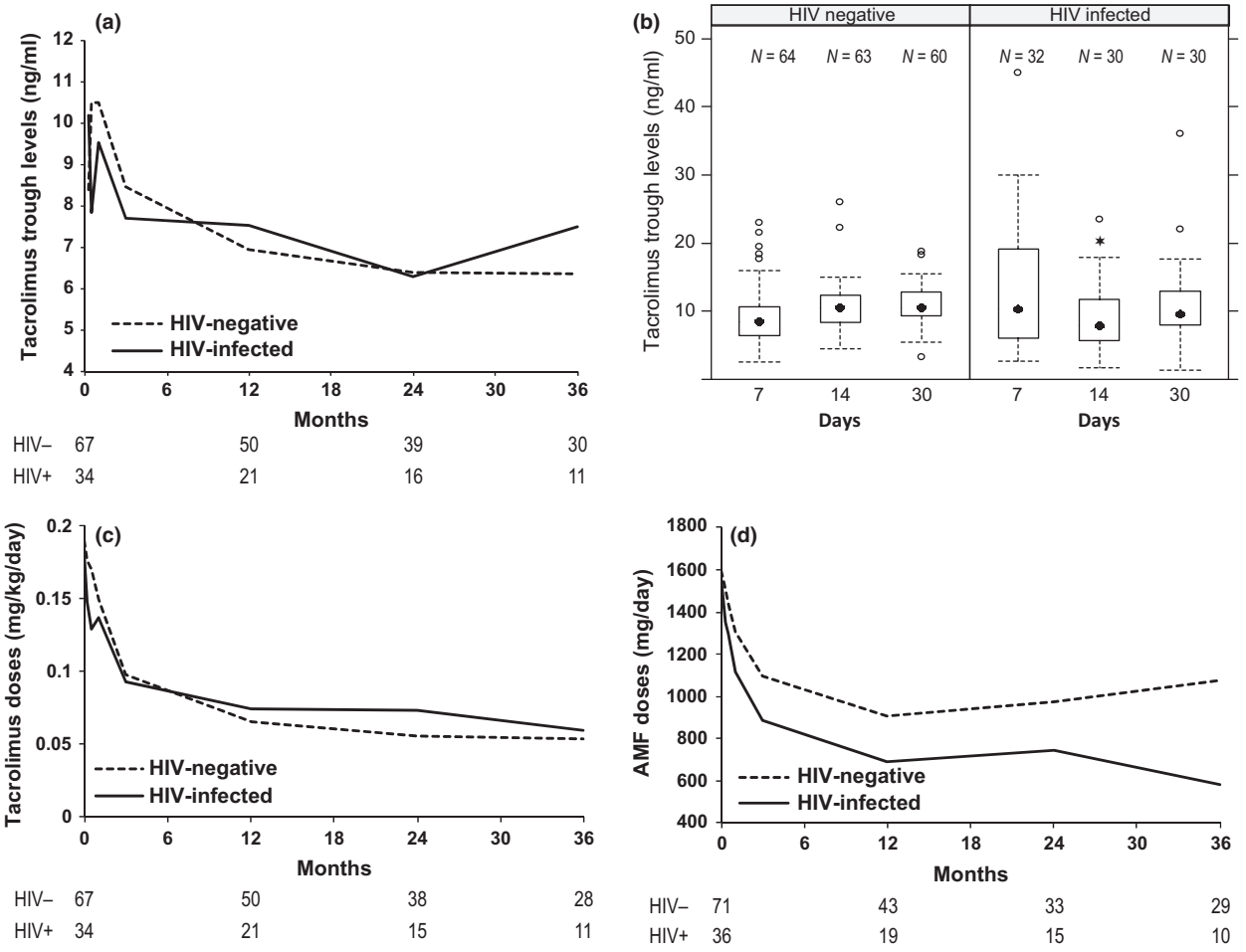

Figure 3 Evolution of immunosuppressive therapy after kidney transplantation (KT). (a) Median tacrolimus trough levels after KT in human immunodeficiency virus (HIV)-infected and HIV-negative recipients ($P = 0.382$). (b) Tacrolimus trough levels in the first month post-transplant (*$P = 0.048$). Data are displayed as the median and interquartile range (IQR) as a skeletal box-whisker plot; the white points represent patients with a median trough level above or below these limits; in HIV-infected recipients, two level values at day 7 and one level value at day 14 post-transplant, greater than 100 ng/ml, have not been possible display in the graph. (c) Mean tacrolimus doses in HIV-infected and HIV-negative recipients ($P = 0.146$). (d) Mean mycophenolic acid (MPA) doses in HIV-infected and HIV-negative recipients ($P = 0.034$). Data of panels a, c, and d were compared between groups by linear mixed-effects models.

interactions with cART [1–6,8]. Although we found no significant differences in rejection rate, the episodes of acute rejection were also more frequent and, significantly, more severe among our HIV-infected recipients, in line with previous American studies [1,2,8]. These pretransplant and post-transplant conditions (prolonged dialysis, acute rejection, DGF), that are so frequent in HIV-infected recipients, are recognized as important graft survival predictors and could contribute to the worse outcomes [10,11,15–18]. In our study, in two-variate Cox analysis for graft loss, HIV infection was not a predictor of graft loss after adjusting for time on dialysis, acute rejection, and DGF. Based on these findings, we hypothesized that a shorter time on dialysis and strategies to minimize the risk of acute rejection and DGF could perhaps improve outcomes.

Few previous publications provide precise data on DGF incidence in HIV-infected recipients [1–4,6,8,9]. Touzot *et al.* reported DGF in only 28% of recipients, while Roland *et al.* reported a 50% incidence of DGF [1,4]. In the noteworthy, National Institutes of Health-sponsored multicenter trial conducted in the USA, including 150 KT infected-HIV recipients, DGF occurred in 46% of patients with KT from deceased donors [2]. In a recent single-center trial, including 92 HIV-infected recipients on sirolimus-based immunosuppression, DGF incidence was 64% and 50% in patients with and without acute rejection, respectively, while the incidence in the general population of American KT recipients on sirolimus is 27% [8,19]. Another very recent study reported 88% DGF incidence in a short series of 11 HIV-infected recipients [9]. Despite

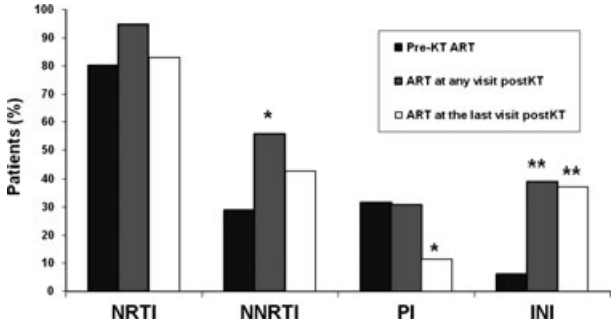

Figure 4 Changes in the main groups of antiretrovirals after kidney transplantation (KT). Columns show percentages of patients receiving any antiretroviral drug within the group indicated, at the time of transplantation, at any visit after transplantation, and at the final follow-up visit. NRTI, Nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI, Non-nucleoside reverse transcriptase inhibitors; PI, Protease inhibitors; INI, Integrase inhibitor (raltegravir); KT, Kidney transplantation. NNRTI: $*P = 0.018$ vs. pre-KT ART. PI: $*P = 0.034$ vs. pre-KT ART. INI: $**P < 0.001$ vs. pre-KT ART.

these data, these previous studies have not highlighted this high incidence [1–4,8,9]. In keeping with those results, we also find a very high DGF frequency. It is known that DGF results in longer hospitalization, higher costs, and decreased long-term graft survival [10,11,17]. Moreover, HIV-infected recipients appear to show an increased susceptibility to the adverse effects of DGF on graft survival [3]. Thus, we have focused our analysis on this important early post-transplant event not examined until now.

Risk factors for DGF observed in our study, such as CIT, recipient age, and HCV seropositivity have also been previously reported in other KT populations [11,20–24]. However, we also found that HIV status is associated with the risk of DGF. Several potential explanations could account for this association between HIV infection and DGF. First, HIV-infected population, in contrast to HIV-negative recipients, shows some clinical characteristics which have a recognized association with DGF development. The duration of pretransplant dialysis, which is usually very prolonged in these patients, has been closely associated with DGF [12,20–22]. Calcified vessels are more frequent in patients with long-term dialysis, which increases the time required for vascular anastomosis. Moreover, persistence of residual renal function, more common in patients with short time on dialysis, has been related with compensatory changes that may promote early graft function [20,25]. However, in our study, time on dialysis has not been identified as a risk factor for DGF. This may be because of the limited sample size. But this could also suggest that other factors not yet established, beyond the known factors associated with DGF, could play a more prominent role in the development of DGF in this population. On the other hand, increased recipient BMI is a known risk factor for DGF and, however, our HIV-infected recipients developed more DGF despite their significantly lower BMI [22].

Second, HIV itself could condition an inherently defective adaptation against the process of ischemia-reperfusion injury. Chronic conditions of the recipient such as viral infections have been previously associated with ischemia-reperfusion injury through generation of reactive oxygen species and heat shock proteins that would contribute to maintain the oxidative stress [26]. The process of postischemic reperfusion is associated with inflammation and increased immunogenicity that leads to acute tubular necrosis and/or rejection [26,27]. HIV infection is known to be associated with stimulated oxidative stress and decreased antioxidant response as well as other immunomodulatory effects that might boost or maintain the graft injury after the reperfusion [2,8,12,28]. This is also consistent with the higher incidence of acute rejection observed in this population [1,2,4–8]. Interestingly, another chronic viral infection such as HCV infection has also been associated with a greater incidence of DGF, acute rejection, and graft loss [23,24].

Third, HIV-infected recipients have an increased risk of drug-related nephrotoxicity [3,12]. Tenofovir, didanosine and stavudine, among others, are associated with nephrotoxicity, especially tubular toxicity [12]. On the other hand, the nephrotoxic effects of calcineurin inhibitors (CNIs) are well known. Concomitant administration with some antiretrovirals, especially protease inhibitors, causes high CNI trough levels which could favor the development of nephrotoxicity and ultimately DGF [1–9,12].

Previous publications have emphasized the difficulty of immunosuppressive therapy management in HIV-infected recipients because of complex drug interactions. However, until now, data have only been reported on doses and levels of immunosuppressive drugs from the first month after KT [1–6,9]. We have placed special emphasis on analysis of the first week post-transplant because DGF and most rejection episodes occur in this period. Our HIV-negative recipients attained adequate tacrolimus trough levels without sudden changes during this early period. On the contrary, HIV-infected recipients tacrolimus levels were very high in the first week and, then the required dosing modifications led to a lower exposure to immunosuppressive drugs in the second week, which perhaps could contribute to DGF or acute rejection development, as has been suggested in other studies [1–3,8]. However, despite these differences between the two groups, tacrolimus levels were not an independent risk factor for DGF in our multivariate analysis.

Our study also provides, for the first time, data on the post-transplant changes of MPA therapy. In HIV-infected recipients, we found a gradual decrease in the MPA doses, suggesting a poor drug tolerance. MPA shares myelotoxicity

and adverse gastrointestinal effects with some antiretrovirals [12]. In addition, HIV itself is likely mediator of abnormal hematopoiesis in all cell lines [29]. All these factors may have possibly forced a decrease in the MPA dosage which could also contribute to the increased incidence of rejection observed in HIV-infected recipients.

To avoid drug interactions, cART including raltegravir is being recently recommended as the first-choice regimen in HIV-infected recipients [1,4,5,30,31]. So far, a detailed description of post-transplant changes in ART was not available. According to these recommendations, indeed we have observed that the use of protease inhibitors decreased, while the use of other antiretroviral drugs without interactions with CNIs (raltegravir) or with weaker interactions (non-nucleoside reverse transcriptase inhibitors) increased after KT. In addition, our data also suggest that, in HIV-infected KT recipients, raltegravir is well tolerated.

The main limitation of our study is the sample size which must be taken into account when interpreting the results. However, all the studies published on HIV-infected KT recipients included a limited number of patients, especially in Europe, where our series is the more extensive. In spite of this, our results for survival and early graft dysfunctions are quite similar to those reported in the more extensive American studies [1–3,8]. Another study limitation is the lack of data on other DGF risk factors –such as donor creatinine or warm ischemia time. These donor factors or some differences in the management of immunosuppressive and ART might explain the lower incidence of DGF reported by Touzot *et al.* [4]. In the French study all patients received induction therapy, and protease inhibitors were withdrawn and raltegravir was introduced in a significant number of patients. These differences may have contributed to the lower acute rejection and DGF incidence observed in their HIV-infected KT recipients. In addition, as in other previous studies, in our experience HCV infection is an important risk factor for DGF, and 42% of our patients are HCV-positive compared to 7% in the French series.

In summary, KT outcomes in HIV-infected recipients are, at least, similar to those from other risk groups. Potentially modifiable pre-transplant factors –such as time on dialysis– and post-transplant factors –such as DGF and acute rejection – could influence KT outcomes. We also highlight inadequate immunosuppressant medication adjustments in the first days after KT, in spite of careful monitoring. Efforts to limit development of DGF, such as lower CIT or appropriate donor selection excluding donors with a high risk for developing DGF, use of antiretroviral regimes with less pharmacological interactions immediately after transplantation, and earlier access to KT are of special interest and may improve the outcomes in HIV-infected recipients.

Authorship

AM, AF, SZ, AR-B, CJ, EG, JP, LJ, DB and LG: designed the study, collected and analyzed the data and reviewed the article. AA, CF and AS-F: Collected data and reviewed the article. AM: wrote the article.

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