Kidney transplantation in HIV infected patients

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Abstract

This review article aims at presenting the main considerations on kidney transplantation in HIV-positive patients. Over last decade, after the advent of highly active antiretroviral therapy (HAART), life expectancy in patients infected with the human immunodeficiency virus (HIV) has changed significantly, with a marked decrease in morbidity and mortality rates in this population. In this setting, the numbers of HIV-positive patients with end-stage kidney disease requiring dialysis is progressively increasing. In view of this new reality, kidney transplantation, once absolutely contraindicated in such patients, became an alternative as renal replacement therapy. Issues about the use of immunosuppressive agents in this group of patients and their potential action in increasing HIV replication, besides the risk of opportunistic infections and neoplasm development, are widely discussed. However, clinical experience in this field shows that using these drugs in seropositive patients seems to be safe, even with reports of antiretroviral action of some immunosuppressant drugs. Nevertheless, there are few transplantation reports in this population. In summary, literature data suggests that kidney transplantation, following specific selection criteria, seems to be a safe alternative as kidney replacement therapy in this group.

Keywords: HIV; kidney transplantation; kidney chronic disease; highly active antiretroviral therapy; immunosuppression.

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Introduction

Over last decade, after the advent of highly active antiretroviral therapy (HAART), the life expectancy in patients infected by the human immunodeficiency virus (HIV) has changed significantly, with a marked decrease in morbidity and mortality rates in this population[1]. Chronic diseases have become part of HIV infection natural history in this new setting and thus therapeutic management definition for these cases has assumed substantial relevance.

In clinical practice, chronic kidney disease prevalence in HIV-infected patients has increased progressively. Chronic kidney disease may develop as a clinical course and treatment complication in HIV-seropositive patients and may independently affect these patients, similarly to what happens in general population. Currently, chronic kidney disease impacts significantly the clinical course in HIV-positive patients[1]. HIV-related kidney disease is the third cause of end-stage renal disease occurring among African-Americans in the United States[2]. HAART therapy introduction has also increased life expectancy in HIV-positive patient undergoing dialysis[3]. Currently there are about 500 HIV-positive patients receiving renal replacement therapy in Brazil according to *Sociedade Brasileira de Nefrologia* data[4].

In view of this new reality, kidney transplantation, once absolutely contraindicated in such patients, is now considered an alternative renal replacement therapy[5]. The main considerations about kidney transplantation in HIV-positive patients will be shown in this chapter.

HIV and kidney transplantation

Given the significant increase in HIV-positive patients' survival after HAART era, kidney transplantation has been considered an alternative treatment in choric kidney disease in this population. However, many safety- and ethics-related questions about organ transplantation in seropositive patients have been raised.

Questions about living donors and allocation criteria from deceased donors to the patients are still under discussion[6]. Organ allocation from HIV-positive deceased donors to seropositive patients has been used in some studies, but cases of superinfection have been reported and this practice has been abandoned[7].

Kidney transplantation from living donors can be performed in HIV-positive patients. However, donors are recommended to be informed that organ transplantation in HIV-infected patients is a recent alternative therapy in clinical practice[8].

Another preoccupant aspect concerning transplantations in this patient group is the need for using immunosuppressive drugs with the possible action to increase HIV replication, besides the risk of opportunistic infections and neoplasm development. Clinical experience in this field, however, shows that the use of these drugs in seropositive patients appears to be safe. The main aspects concerning kidney transplantation in this population are introduced as follows.

Kidney transplantation – Pre-HAART era

Before the advent of HAART era, reports about HIV-positive patient kidney transplantation were limited to either isolated case reports or small numbers of patients. One of the first publications was released in the early 90s by the University of Minnesota, reviewing 11 HIV-positive patients undergoing kidney transplantation. Results showed a 36% mortality rate. One patient died from sepsis two months after the transplantation and three patients developed AIDS and died within 13 months. The graft survival rate in 30 months was 54%[9]. Time to progression to AIDS was evaluated by Tkazis *et al.* in three HIV-positive patient groups with the objective to study immunosuppression impact on kidney transplantation in HIV-infected patients: kidney transplanted patients (n = 25), hemophiliacs (n = 42), and patients infected after blood transfusion (n = 28). There was a trend to earlier AIDS development (15 months) in transplanted patients (16%) than in the two other groups. However, from the 15th month on, the trend to AIDS development was the same in the three groups, reaching statistical significance from de fifth-year follow-up[10].

The largest kidney transplantation in positive HIV review over the pre-HAART period was obtained from USRDS (United States Renal Data System) data, analyzing kidney transplantations performed between 1987 and 1997. The results showed worse patient survival rate in the fifth year post-transplantation (71% vs 78% in control group) and kidney graft (44% vs 61% in control group). In multivariate analysis, HIV infection was listed as independent mortality factor for recipients from deceased donors, as well as for graft loss[11]. These results substantiated the indication restriction of kidney transplantation in HIV-positive patients.

Kidney transplantation – Post-HAART era

In the late 90s, with the advent of HAART era, there was a great improvement in morbidity and mortality related to HIV-positive patients. This improvement also mirrored in mortality rates for HIV-positive patients on dialysis, which were significantly reduced, coming to equalize the mortality rate in HIV-seronegative patients in dialysis programs. The survival rate for HIV-positive patients on dialysis raised from 56% (before 1990) to 74% (late 90s)[12].

These results led to a re-evaluation of kidney transplantation as treatment option in HIV-positive patients with severe chronic kidney disease. One of the first reports was made by Stock *et al.*[13], from the University of California. To become eligible for kidney transplantation, HIV-positive patients had to fulfill the following criteria: undetectable viral load (negative HIV-RNA in plasma) for

three months, CD4+ T cell counts > 200 cells/mm^3 for six months, and neither opportunistic infection nor carcinoma. Ten patients undergoing kidney transplantation were included. At 36-month follow-up, all of them were alive and had a functioning graft. The kidney graft rejection rate was 50%. All of the patients were maintained on HAART. Viral load remained undetectable in all patients and CD4 cell counts remained stable. These results were encouraging to indicate kidney transplantation as a treatment option in HIV-positive patients with well-controlled disease. There were several other reports strengthening this treatment alternative (Table 1).

In 2003, Roland *et al.*[14] reviewed 26 seropositive patients receiving kidney transplantation. Survival rates for the patient (92%) and the graft (85%) in 10 months were comparable to HIV-negative patient rates. The rejection rate in HIV-infected patients was 37%. The review of the USRDS registry data for deceased donor kidney transplantation in the period 1996 to 2001 showed that from 27,851 patients with available HIV serology only 47 patients (0.2%) were HIV-positive. From these, 12.8% were black. HIV-positive patient survival rate after three years was 95%. Only 2 HIV-positive patients died (4.3%), compared to 12.8% in the HIV-negative group. These good results might have been influenced by stricter criteria from transplanting centers in selecting HIV-positive recipients for kidney transplantation. Another possible bias in this review might have been the increased use of immunosuppressive induction therapy in seropositive recipients.

From these results, the authors proposed kidney transplantation in HIV-positive patients as a more viable treatment strategy after HAART era advent.

In a prospective study, Kumar *et al.*[2] studied 40 HIV-positive kidney transplanted subjects. Inclusion criteria were similar to those described by Stock *et al.*[13] (negative HIV-RNA, viral load < 400 copies/mL, and absolute CD4+ cell count > 200 cells/mm^3). The results showed that patient survival rate over first and second post-transplanta-

Table 1 – Patient and kidney graft survival in positive-HIV patients undergoing kidney transplantation

Authors	n	Follow-up time (months)	Patient survival	Graft survival
		before HAART		
Tzakis *et al.*[10] (1990)	5	36	80%	80%
Erice *et al.*[9] (1991)	11	30	64%	54%
Swanson *et al.*[11] (USRDS data) (2002)	32	60	71%	44%
		after HAART		
Stock *et al.*[13] (2003)	10	16	100%	100%
Roland *et al.*[14] (2003)	29	10	92%	85%
Abbott *et al.*[15] (USRDS data) (2004)	47	36	95%	97.3%
Kumar *et al.*[2] (2005)	40	24	82%	71%
Qiu *et al.*[16] (UNOS data) (2006)	38	60	91.3%	76.1%
Roland *et al.*[19] (2008)	18	36	94%	83%
Gruber *et al.*[18] (2008)	8	15	100%	88%
Locke *et al.*[17] (UNOS data) (2009)	100	12	95.4%	87.9%

USRDS, United States Renal Data System; UNOS, United Network for Organ Sharing.

tion years was 85% and 82%, respectively, similar to results obtained from other high risk patient groups and larger than survival rate in HIV-positive patients on dialysis.

Qiu *et al.*[16] analyzed kidneys from the same deceased donor transplanted to HIV-positive or HIV-negative patients, these data were obtained from United Network for Organ Sharing (UNOS) from 1997 to 2004. Thirty-eight HIV-positive patients and 38 HIV-negative patients receiving kidneys from the same donors were included in this analysis. Although the results were statistically non-significant, the patient and graft survival rate was higher in the HIV-positive group, compared to the HIV-negative group.

More recently, Locke *et al.*[17], at John Hopkins Medical Hospital, have analyzed 39,501 kidney transplanted patients from the UNOS registry from 2004 to 2006 and they showed that although patient survival is similar in HIV-positive and HIV-negative, graft survival was significantly lower in HIV-positive cases (87.9% vs 94.6% in HIV-positive).

A group from University of Detroit evaluated the influence of HIV-positive recipient characteristics on kidney transplantation and reported a clinical course analysis of eight kidney transplanted seropositive patients with other poor prognosis factors, such as coinfection with hepatitis C virus and immune sensitization over a mean time of 15 months. The survival rates found were 100% for the patient and 88% for the graft at the end of the period. In this study, only one patient developed acute rejection (13%)[18].

On the other hand, high acute rejection rates in HIV--positive transplanted subjects were described by Roland *et al.*[19] in a study assessing 18 patients undergoing kidney transplantation. The authors described a 52% acute rejection incidence over the first-year follow-up and 73% in three years, which is consistent with the results previously found by *et al.* in 2003.

There are no specific registries about transplantation activity in HIV-positive patients in Brazil. Recently, we have performed a kidney transplantation in a 61-year-old patient presenting with a chronic kidney disease secondary to polycystic kidney disease; he had been infected with HIV seven years before the transplantation[20]. At the time of HIV infection diagnosis, the patient received antiretroviral therapy with zidovudine (AZT®, AstraZeneca) 600 mg/day, 3Tc (lamivudine; Epivir®, GlaxoSmith) 75 mg/day and atazanavir (Reyataz®, Bristol-Myers Squibb) 400 mg/day. He was responsive to the therapy and, six months after starting it, he had undetectable viral load, which was maintained throughout evolution. CD4+ lymphocyte counts was also kept above 500 cells/mm^3. In the course of the disease, the patient presented with end-stage renal disease, for which he had been receiving treatment with hemodialysis for the last five and a half years. At the transplantation time, his HIV-RNA was negative and CD4+ lymphocyte count was 464 cells/mm^3. Kidney transplantation performed with live donor was uneventful and the patient showed an immediate reduction in serum creatinine.

The immunosuppressive regimen included basiliximab (Simulect®, Novartis) as inducing drug and cyclosporine (Sandimmun®, Novartis), sirolimus (Rapamune®, Wyeth), and prednisone as maintenance drugs. Although the patient had been given only half the usual doses of cyclosporine and sirolimus, he had blood levels extremely high. Trough concentration was 1,131 ng/mL for cyclosporine and 56.1 ng/mL for sirolimus 6 days after using the drugs, with dosage being adjusted to 25% of usual dosage. Currently, two years after kidney transplantation, the patient is well, with good kidney graft function, undetectable viral load, and CD4+ lymphocyte count of 645 cells/mm^3.

Regarding HAART era benefits, kidney transplantation in HIV-infected patients is considered an alternative treatment, which tends to occur more frequently in clinical practice.

In view of this new reality, establishing criteria for organ transplantation practice in this population is required. Recently, based on major impact studies on kidney transplantation in HIV-infected patients, Bhagani *et al.*[8] have gathered the main recommendations to consider a patient as a receptor candidate (Table 2).

Table 2 – Selection criteria in HIV-positive patients for kidney transplantation

• CD4+ lymphocyte count > 200 cells/mm3 for at least 6 months
• Undetectable viral load (< 50 RNA copies/mL) for at least 6 months
• Treatment using HAART for at least 6 months
• No AIDS-defining diseases following HAART start

HIV and immunosuppression in kidney transplantation

Overall, immunosuppressive drug use in organ transplantations in HIV-infect patients has proven to be effective and safe, since some of these drugs also have an antiretroviral action. Because of drug-drug interaction between some HAART drugs and immunosuppressive agents, blood level monitoring of immunosuppressive drugs should be done more often, with dosage adjustments whenever necessary[21].

Immunosuppressive drug antiretroviral effect

For many years had HIV infection been considered a contraindication to organ transplantation based on a principle that, in the presence of immunosuppression, there would be an environment favoring viral replication. However, more recently, studies have demonstrated that some of the immunosuppressive drugs used in transplantation, such as calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus, and mycophenolic acid, exhibit antiretroviral action.

Cyclosporine is a calcineurin inhibitor with properties able to inhibit HIV replication. This effect is a result of cyclosporine binding to cyclophilin A, preventing the formation of protein p55Gag/cyclophilin complex, required for HIV maturation and replication. HIV is known to replicate only in activated CD4 T cells. Considering cyclosporine inhibits T cell activation via IL-2 inhibition, this drug can reduce activated CD4 T cell number, thus reducing CD4+ T cell pool available to viral replication[22]. Cyclosporine possibly has an antiapoptotic effect on CD4+ T lymphocyte, as demonstrated by Groux *et al.*[23] In this study, T lymphocyte apoptosis was prevented by cyclosporine A in peripheral blood samples from HIV-positive subjects *in vitro*.

Tacrolimus action as a antiretroviral drug was shown in few studies. Tacrolimus action inhibiting viral proliferation was described by Briggs *et al.*[24] in HIV-chronically infected cells.

Sirolimus is an immunomodulation-acting immunosuppressive drug inhibiting mTOR (mammalian target of rapamycin). The drug can reduce CCR5 viral co-receptor expressed in T lymphocytes and monocytes at a transcriptional level. CCR5 receptor is essential for HIV transmission and replication, as evidenced by the fact that individuals not expressing this protein proved to be resistant to HIV infection.

Azatioprin use has been associated with increased viral replication, while the opposite seems to happen with the use of mycophenolate mofetil[26]. The mycophenolic acid prodrug mycophenolate mofetil (MMF) is another immunosuppressive drug showing antiretroviral effect. The drug seems to have synergistic activity on the nucleoside analog reverse transcriptase inhibitors, one of the classical components used in HIV infection treatment regimen. This synergism results from desoxyguanosine-triphosfate, an intracellular enzyme essential for HIV replication[27].

Izzedine *et al.*[26] showed prednisolone increases CD4+ T lymphocyte population. Another study showed prednisolone acts by suppressing HIV viral load and inhibiting CCL2, a proinflammatory cytokine induced by HIV infection[28].

As for the use of either monoclonal or polyclonal anti-CD3 antibodies, it is worth noting it is not recommended in HIV-positive patients. It is a powerful immunosuppressive drug capable of inducing CD4+ T lymphocyte depletion, increasing the risk of disease progression, as well as opportunistic infection development[29].

Drug interactions between immunosuppressive agents and HAART

Concurrent use of immunosuppressive and antiretroviral drugs is required in an organ transplantation setting in HIV-positive recipients. Complex pharmacokinetic and pharmacodynamic interactions between these drugs are described in literature and therapeutic level strict monitoring is required both to keep HIV infection controlled and to avoid rejection and toxicity by immunosuppressive drugs.

The most classical interactions are found between common protease inhibitors used to treat HIV-positive patients and calcineurina inhibitors (cyclosporine and tacrolimus) or mTOR inhibitors (sirolimus and everolimus). This interaction results from the fact both protease inhibitors and immunosuppressive drugs previously described are metabolized via P450 cytochrome, contributing to increasing immunosuppressive blood levels[30]. In literature, HIV-positive patients are suggested to initiate calcineurin inhibitors four weeks before transplantation (in case of living donor transplantation), monitoring drug levels to pre-transplant setting. This management aims to enable transplantation in the presence of immunosuppressants therapeutic levels, minimizing the risk of toxicity or, less frequently, underexposure to the drug[8].

Given the pharmacological interactions that promote increased blood levels of calcineurin inhibitors and mTOR inhibitors, we must emphasize the elevated risk of toxicity of these drugs, including the possibility of thrombotic microangiopathy development. Thrombotic microangipathy is a histological manifestation of hemolytic-uremic syndrome, occurring as a post-transplantation complication in an incidence ranging from 0.8% to 14% kidney transplantations. We should add to this the fact that HIV infection is a proven risk factor for thrombotic microangiopathy development[31]. Recently, cases of hemolytic-uremic syndrome associated with sirolimus use were reported[20,32], possibly resulting from reduced VEGF (an important factor in maintaining vascular endothelium viability) expression induced by sirolimus[33]. Furthermore, there is evidence that high sirolimus blood levels associated with cyclosporine also contribute to the thrombotic microangiopathy pathogenesis[34].

Sodium mycophenolate[20] and mycophenolate mofetil[21] are considered safe immunosuppressive alternatives for kidney transplantation in HIV-positive patients, as they have few interactions with other common drugs used in HAART. However, diarrhea, a well-known mycophenolate side effect, may hinder its use in clinical practice, since it can be added to the diarrheal effects of antiretroviral drugs and the disease itself in these patients.

Despite the increasing need for association between immunosuppressants and antiretroviral drugs in current clinical practice, there are few studies to guide the safe use of these drugs combined. Potential drug interactions between the main immunosuppressive drugs used in organ transplantation setting and major antiretroviral drugs are shown in Table 3.

Table 3 – Potential interactions between antiretroviral and immunosuppressive agents

HAART		Immunosuppressive drugs							
		OKT3 ATG	Anti-IL2R	CsA	TAC	AZA	MMF	SRL	Corticosteroids
NRTIs	Lamivudine	c.i.	n.a.	0	0	0	+	0	0
	Estavidine	c.i.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Zalcitabine	c.i.	n.a.	0	0	n.a.	n.a.	0	n.a.
	Didanosine	c.i.	n.a.	0	0	n.a.	+	0	n.a.
	Zidovudine	c.i.	n.a.	0	0	n.a.	-	0	n.a.
	Abacavir	c.i.	n.a.	n.a.	n.a.	n.a.	+	n.a.	n.a.
NNRTIs	Delavirdine	c.i.	n.a.	+	n.a.	n.a.	n.a.	+	+
	Efavirenz	c.i.	n.a.	-	n.a.	n.a.	n.a.	-	-
	Nevirapine	c.i.	n.a.	-	n.a.	n.a.	n.a.	n.a.	-
Protease Inhibitors	Amprenavir	c.i.	n.a.	±	±	0	n.a.	±	-
	Indinavir	c.i.	n.a.	+	+	0	n.a.	±	-
	Lopinavir	c.i.	n.a.	±	±	0	n.a.	n.a.	-
	Nelfinavir	c.i.	n.a.	±	+	0	n.a.	±	-
	Ritonavir	c.i.	n.a.	+	+	0	n.a.	+	+
	Saquinavir	c.i.	n.a.	+	+	0	n.a.	±	-
	Enfuvirtide	c.i.	n.a.	0	0	n.a.	n.a.	n.a.	n.a.
	Tenofovir	c.i.	n.a.	n.a.	0	n.a.	-	n.a.	n.a.

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OKT3, anti-CD3 monoclonal antibody; ATG, antithymocyte globulin; Anti IL2-R, anti-interleucin-2 receptor antibodies; AZA, azatioprine; CsA, cyclosporine; FK, tacrolimus; MMF, mycophenolate mofetil; SRL, sirolimus; c.i., contraindicated; n.a., not assessed; 0, no interaction; +, positive interactions; –, negative interactions; ±, theoretically, interactions can occur.

Conclusion

HIV-seropositivity is no longer absolutely contraindicated in kidney transplantation, but it is currently a relative contraindication[35]. Nevertheless, there are still few reports on transplantation in this population.

In summary, although some studies show a trend towards higher graft rejection rates in HIV-positive patients, literature data suggests kidney transplantation following specific selection criteria seems to be a safe alternative to renal replacement therapy in this group.

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