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CLINICAL STUDY

The first kidney transplantation in an HIV positive recipient in Slovakia

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ABSTRACT

Patients infected with human immunodeficiency virus (HIV) have long been considered unsuitable candidates for solid organ transplantation due to their poor prognosis. After the introduction of combination antiretroviral therapy, the survival of this group of patients improved significantly. HIV positive patients had been successfully transplanted for the last 18 years. HIV positive patients encounter very specific issues after transplantation, specifically related to drug interactions and higher rejection rates. Despite that, HIV positive patients have similar results to HIV negative patients post transplantation.

We present the case of the first kidney transplantation in an HIV positive patient in Slovakia. The procedure was possible due to a change in legislation, as HIV positivity was an absolute contraindication for transplantation in Slovakia until October 2023. The aim of our case report is to draw attention to the possibility of kidney transplantation in an HIV positive patient and to the specific problems related to the preparation of an HIV positive patient for transplantation, post-transplant complications and the possibilities of their management *(Fig. 6, Ref. 37)*. Text in PDF www.elis.sk

KEY WORDS: kidney transplantation, HIV, human immunodeficiency virus, acute rejection, HAART, drug interaction.

Abbreviations: AIDS – Acquired immune deficiency syndrome, AR – Acute rejection, ART – Antiretroviral therapy, BKV – BK polyomavirus, CKD – Chronic Kidney Disease, CNI – Calcineurin inhibitor, cp – Copies, CS – Corticosteroids, eGFR – Estimated glomerular filtration ratio, ESRD – End stage renal disease, CMV – Cytomegalovirus, CYP – Cytochrome, DNA – Deoxyribonucleic acid, eGFR – Estimated glomerular filtration rate, EIA – Enzyme immunoassay, HAART – Highly active antiretroviral therapy, HBV – Hepatitis B virus, HCV – Hepatitis C virus, HD – Hemodialysis, HIV – Human Immunodeficiency Virus, HIVAN – HIV-associated nephropathy, HLA – Human leukocyte antigen, IgG – Immunoglobulin G, INI – Integrase inhibitor, IS – Immunosuppressive treatment, i.v. – Intravenously, KDIGO – Kidney disease improving global outcomes, MPA – Mycophenolic acid, 6-MP – 6-metyplrednisolone, mTOR – Mammalian target of rapamycine inhibitor, NNRTI – Non-nucleoside reverse transcriptase inhibitor, PCR – Polymerase chain reaction, PI – Protease inhibitor, RB – Renal biopsy, RNA – Ribonucleic acid, RRT – Renal replacement therapy, TAC – Tacrolimus, TCMR – T-cell mediated rejection, TCMR BL – T-cell mediated rejection border-line

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Introduction

Human immunodeficiency virus (HIV) infection was traditionally considered an absolute contraindication for transplantation because of the concern that immunosuppression would accelerate HIV disease progression, resulting in an increased mortality and "waste" of organs.

Since potent antiretroviral therapy (ART) became widely available in 1996 (1), the prognosis of patients with HIV infection has dramatically improved. There have been significant decreases in morbidity and mortality, and, for many individuals with well-controlled viral replication, HIV is now a chronic, manageable disease (2, 3). HIV positive patients had been successfully transplanted for the last 18 years. HIV positive patients encounter very specific issues after transplantation, specifically related to drug interactions and higher rejection rates. Despite that, HIV positive patients have similar results to HIV negative patients post transplantation (4).

Chronic kidney disease (CKD) secondary to HIV infection is a common problem. The spectrum of renal pathology in HIV positive patients includes lesions directly related to intrarenal HIV

gene expression and lesions related to co-morbidities, drug effects, immune dysregulation, and other co-infections (5). Two most common manifestations of HIV in the kidney are podocytopathy and immune complex-mediated glomerular disease. The podocytopathy can manifest as focal segmental glomerulosclerosis or minimal change disease and diffuse mesangial hypercellularity (6). HIV associated nephropathy (HIVAN) is most prevalent in patients who receive antiretroviral therapy (ART) late after initial diagnosis (4, 7). Early initiation of highly active antiretroviral therapy (HAART) leads to improved prognosis of HIV patients, decreased morbidity and mortality in HIV-positive patients (8). Estimating the burden of CKD in HIV positive patients is important when considering the dialysis and transplantation. It is important to understand the benefits of transplantation in the HIV infected population. Because of the improved quality of life and better long-term prognosis of a HIV positive patient, the focus of treatment for these patients has moved to transplantation rather than dialysis (4). The growing experience of centers performing transplantations in HIV positive patients and their good outcomes have outweighed the concerns about the impact of immunosuppressive therapy on HIV replication and the incidence of other infections after transplantation (9). HIV infection has ceased to be considered an absolute contraindication to kidney transplantation in many centers (10).

HIV positive patients should be selected for transplantation according to standard selection criteria, similar to HIV negative transplant recipients (11). There are no established HIV-specific selection criteria for recipients, but most centers follow the patient selection criteria set forth in a National Institutes of Health multicenter trial, which specified that patients must have an undetectable viral load and a $CD4^+$ T lymphocytes count of > 200 cells/uL (microliter) on a stable antiretroviral therapy (ART) regimen for at least six months (12).

Loss of HIV control and progression to advanced HIV have not been observed in the larger series of HIV positive patients following transplantation and immunosuppression, provided they had good viral control and were maintained on a stable antiretroviral regimen pretransplant (13). Important prerequisites for transplantation in an HIV positive patient are adherence to treatment, a stable HAART regimen, absence of Acquired Immune Deficiency Syndrome (AIDS) symptoms, use of barrier contraception, and in the case of co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), histologically proven absence of cirrhosis (14, 15, 16, 17). All potential recipients should routinely be screened for tuberculosis, syphilis and hepatitis B and C pre-transplant. Treatment for co-infection with HBV/HCV should be done prior to transplantation (4).

Because of the interaction between protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) with the calcineurin inhibitors (CNI) and mTOR inhibitors, it should be not easy to manage the patients on these drug combinations. Drug levels vary between patients and often CNI dosages in the patients on NNRTI must be significantly higher, in patients on protein inhibitors lower, as a result of the effect of these drugs on the cytochrome P450 enzyme (CYP3A4). Calcineurin inhibitors, which are mandatory for transplantation, need the same enzyme complex for their clearance. Most NNRTI induce CYP3A4, whereas PI inhibit it. Since this same metabolic pathway is used in the metabolism of CNI and mTOR inhibitors, the use of NNRTI results in the need for higher dosing of those immunosuppressive drugs, whereas the use of PI results in the requirement for significantly lower doses (18, 19, 20, 21). This results in extreme difficulty in adjusting the optimal dose of CNI, for which the therapeutic range is narrow. Integrase inhibitors (INI), potent anti-HIV drugs, are mainly metabolized by uridine diphosphate glucuronosyltransferase 1A1 and do not induce or inhibit CYP3A4. Drug-drug interaction is presumably absent when NNTRI or PI are replaced by INI (21).

Since the patient presented in this case was treated with a triple combination of dolutegravir, darunavir, ritonavir before and at the time of transplantation, and after transplantation the treatment was changed to a double combination of dolutegravir and lamivudine, we provide information about the ARV drugs used.

Dolutegravir, a second generation INI, is an antiretroviral medication used, together with other medication, to treat HIV/AIDS. Dolutegravir is a safe, effective, and well-tolerated treatment option for adults with HIV-1, even in the setting of resistance to other antiretrovirals (22). It may also be used, as part of post exposure prophylaxis, to prevent HIV infection following potential exposure (23).

Darunavir is a nonpeptidic inhibitor of protease that lodges itself in the active site of PI through a number of hydrogen bonds. It was developed to increase interactions with HIV-1 protease and to be more resistant against HIV-1 protease mutations (24).

Ritonavir is an HIV protease inhibitor that interferes with the reproductive cycle of HIV-1. Although it was initially developed as an independent antiviral treatment, it has been shown to possess advantageous properties in combination regimens with other protease inhibitors. Ritonavir is a potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of other protease inhibitors (25, 26).

Lamivudine, is an antiretroviral medication used to prevent and treat HIV/AIDS. It is also used to treat chronic hepatitis B when other options are not possible. It is effective against both HIV-1 and HIV-2. It is typically used in combination with other antiretrovirals such as zidovudine, dolutegravir, and abacavir. Lamivudine may be included as part of post-exposure prevention in those who have been potentially exposed to HIV (27).

In the post-transplantation period, one should keep in mind the higher risk of developing complications such as delayed graft function, AR and infections (28). Rejection remains an important clinical issue in HIV positive patients, despite aggressive induction therapy and immunosuppression. The reason for high rejection rates in HIV positive patients is still not clear. Many people have speculated that the rejection rates are simply related to the drug interactions affecting the cytochrome P450 enzyme. However, a more complex immunological reality might be responsible for high rejection rates in HIV positive patients. Chronic immune activation and inflammation is known to contribute to the risk of cardiovascular diseases in HIV positive patients (29). The exposure

to co-pathogens may result in heterologous immunity, leading to immunologic memory for HLA antigen in the absence of direct exposure. Furthermore, the loss of T helper lymphocytes function in response to antigens and the critical reduction in $CD4^+$ T lymphocytes number might be responsible for a dysregulated immune response in HIV positive patients (29, 30, 31).

Case

We present the case of a 35-year-old patient with end-stage renal failure due to HIV associated nephropathy, who was diagnosed HIV positive in November 2019, when the patient was hospitalized with symptoms of bilateral bronchopneumonia and renal failure, with no history of CKD. Initial serological investigations revealed HIV positivity, and Pneumocystis jirovecii was detected from bronchoalveolar lavage fluid by polymerase chain reaction (PCR), subsequently confirmed microscopically. The patient's clinical condition met AIDS criteria, genetic testing identified a CCR5 homozygote without delta 32 deletion, HLA-B57:01 was negative. At the time of AIDS diagnosis, the HIV load was 415,000 cp/mL and the $CD4^+$ T lymphocyte count was 10 cells/µl. HAART (dolutegravir 50mg/day, darunavir 800mg/day, and ritonavir 100mg/day) and haemodialysis therapy were initiated. Despite improvement in the patient's clinical condition, renal function did not recover; the condition was evaluated as HIV nephropathy, vascular nephrosclerosis, and co-morbidity of excessive protein intake; a renal biopsy was not performed. With continued HAART, HIV RNA replication (PCR) fell below detectable levels in March 2020, $CD4^+$ T lymphocyte count rose to 310 cells/µl of blood. The patient was first referred to the transplant center in April 2021. However, in view of the legislation in Slovakia at that time, the patient could not be placed on the waiting list for kidney transplantation, as HIV positivity was an absolute contraindication to transplantation (32). As the patient had three potential living kidney donors at the time – a friend, his father and an AB0 incompatible sister, the option of transplantation was consulted in the Czech Republic. After receiving a consent opinion, the patient underwent pre-transplantation examinations in the following months, but the transplantation abroad did not take place as the potential donors gradually withdrew from donation for personal or health reasons. In May 2023, the patient was re-consulted along with a 38-year-old isogroup (A, RhD posit.) childhood friend willing to donate a kidney. Since even at this time the legislation in Slovakia did not allow kidney transplantation to an HIV positive patient, the procedure was again communicated in the Czech Republic. The couple was accepted on the condition that the examinations and procedures would be covered by health insurance in Slovakia. At the same time as the requests to the respective health insurance companies, the pre-transplant examinations of the kidney recipient were updated and the examinations of the potential donor were performed, and the opinion of the Ethics Committee at the Ministry of Health of the Slovak Republic was requested. After meeting the medical and psychosocial conditions and with a positive opinion of the ethics committee, the only obstacle to treatment abroad was the promise of reimbursement by the respective health insurance companies of the patient and the potential donor. A major reversal was brought about by a change in legislation and the removal of HIV positivity from the absolute contraindications to kidney transplantation in October 2023 (33). In the following two months, investigations including human leukocyte antigen (HLA) system typing, anti-HLA antibody screening by Luminex, antiendothelial antibody and crossmatching by complement-dependent lymphocytotoxicity were completed. The results of immunological tests were negative, the compatibility index was 26. Detailed serological screening revealed hepatitis B with seroconversion (anti-HBc total pos., HBsAg neg.) of unclear time of onset, HBV DNA (PCR) testing in the reference laboratory was negative. As of March 2020, HIV viral load was undetectable, $CD4^+$ T lymphocyte counts had not fallen below 200 cells/µL of blood. Protective IgG against cytomegalovirus (CMV) prior to transplantation was positive in both the patient and the kidney donor.

Patient underwent primary kidney transplantation from a living donor on 6.12.2023. Baseline admission characteristics of the recipient included residual diuresis of 300ml, BMI was 23.5 kg/m^2, patient was treated for high blood pressure and secondary hyperparathyroidism. Immunosuppressive therapy was initiated two days before surgery – tacrolimus (TAC) orally at a single daily dose of 0.2 mg/kg (day –2) and 0.1 mg/kg (day –1), mycophenolic acid (MPA) orally 720 mg per day. Two doses of basiliximab of 20 mg each (on day 0 and day 4) were administered intravenously (i.v.) as a part of the induction, together with 500 mg of 6-methylprednisolon (6-MP) i.v. during surgery. A combination of prednisone 20mg/day orally, and mycophenolic acid 1440 mg/day orally followed the induction treatment. Tacrolimus was interrupted because of high trough blood concentration (TAC > 30 ng/mL) on the day of transplantation (day 0). There were no surgery complications, cold ischemia time was 195 minutes. Primary onset of graft func-

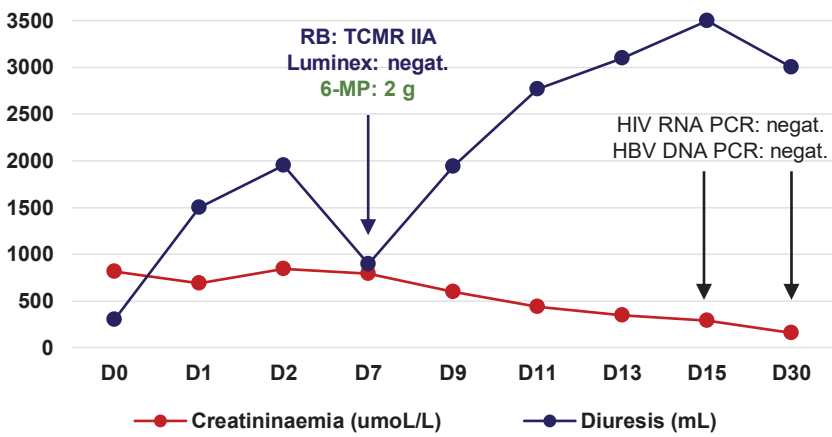

Fig. 1. The course of graft function and diuresis in the first month after transplantation.

tion was noted (Fig. 1). Prophylaxis against Pneumocystis Jirovecii and toxoplasmosis was provided by the use of trimethoprim-sulfamethoxazole. This agent also provides prophylaxis against urinary tract infections.

The early post-transplant period was complicated by acute kidney injury of the graft. Although tacrolimus treatment was discontinued from the day 0, trough blood concentration above 30 ng/mL continued for next three days (Fig. 2).

An initial increase in diuresis and a decrease in creatininaemia was followed by a sudden worsening of graft function (Fig. 1, Fig. 3). Early causes of graft dysfunction such as hemorrhage, vascular cause, ureteral obstruction, and uroinfection were ruled out in the differential diagnosis. Screening for donor specific antibodies by Luminex method was negative. Persistent high tacrolimus trough blood concentration supposed an acute CNI graft toxicity. Out of concern for the development of oligoanuric AKI in the graft and possible activation of HIV/HBV viruses during overimmunosuppression, a single dose of rifampicin (600mg orally), which is a strong CYP inducer, was administered on day 4 (34). Administration of rifampicin led to a rapid decline of tacrolinemia (Fig. 2); from day 6, TAC was added back to maintenance immunosuppression at a single daily dose of 1mg gradually titrated to 0.5mg every other day. As only a slight improvement in graft function was noted after the decrease in tacrolinemia, a renal biopsy was performed on day 7 with the finding of acute T-cell mediated rejection (TCMR) Gr. IIA and a good response to the administration of 6-MP i.v. at a total dose of 2000mg (Fig. 3).

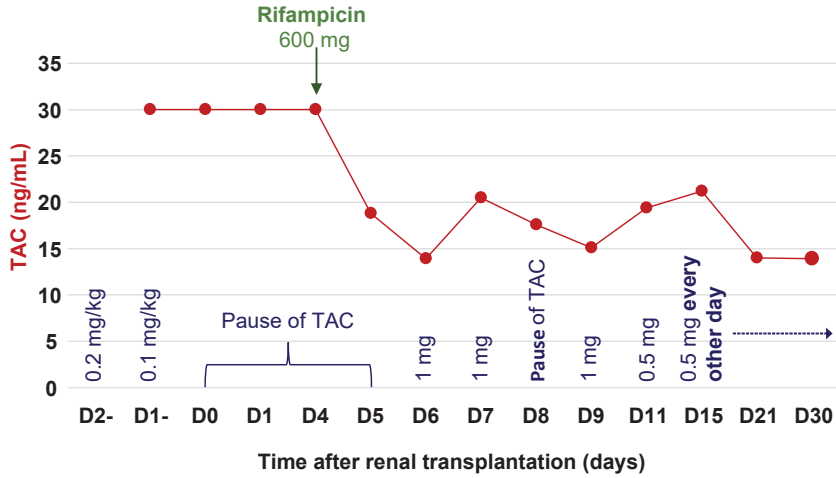

Fig. 2. Trough blood concentration of tacrolimus in the first month after transplantation.

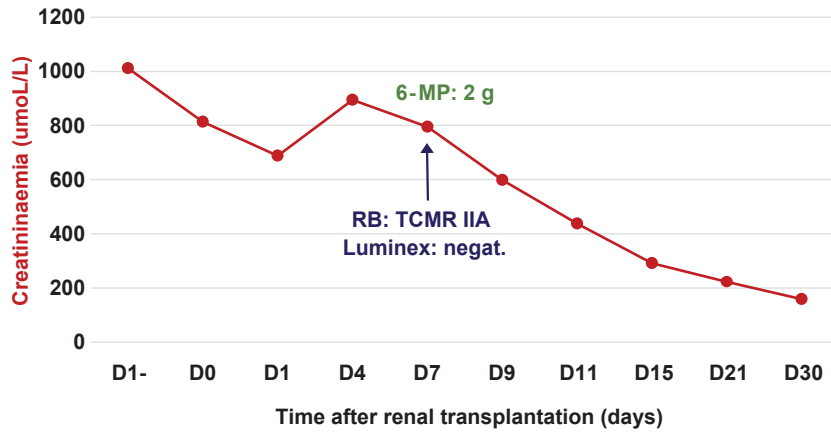

Fig. 3. The course of graft function in the first month after renal transplantation.

In the following period, the patient's condition developed without complications except for the development of lymphocele, the daily dose of TAC was adjusted to 0.5mg every other day, and the patient with improving graft function was demitted on postoperative day 16. The lymphocele did not require surgical intervention, and spontaneous resorption occurred during follow-up. Regular monitoring of opportunistic infections without detection of BKV DNA (PCR), HIV RNA (PCR) and HBV DNA (PCR) replication, two months after transplantation a positive finding of CMV DNA (PCR), for which pre-emptive treatment with valgancyclovir was initiated. No urinary tract infection or other bacterial or mycotic complication was noted. Despite the modified TAC dose, trough concentration of the drug persisted above 11 ng/mL. An infectiologist was consulted about changing HAART to a treatment with weaker interference with CNI. On posttransplant day 73, antiretroviral therapy was modified to a combination of dolutegravir and lamivudine, which was followed by a rapid decline in trough concentration of TAC and the need to increase the dose up to 8 mg/day over three weeks (Fig. 4).

Due to the finding of TCMR borderline (TCMR BL) in the control/protocol graft biopsy, 6-MP was administered i.v. at a total dose of 1000mg (Fig. 5).

The evolution of $CD4^+$ T lymphocytes shortly before and after transplantation in relation to immunosuppressive regimens (induction, maintenance immunosuppression and antirejection therapy) is shown in Figure 6. At the end of the third month after transplantation, graft function was stable, creatininemia was stagnant between 130 and 140 umoL/L, eCKD was 1.01ml/s/1.73 m^2, proteinuria was 0.45 g/24h and CD4+ lymphocytes numbered 100 cells/uL. The patient felt well, and from the 6^{th} post-transplant week he returned to work.

Discussion

This case report illustrates that kidney transplantation may be a good treatment option for stable HIV patients. Our patient

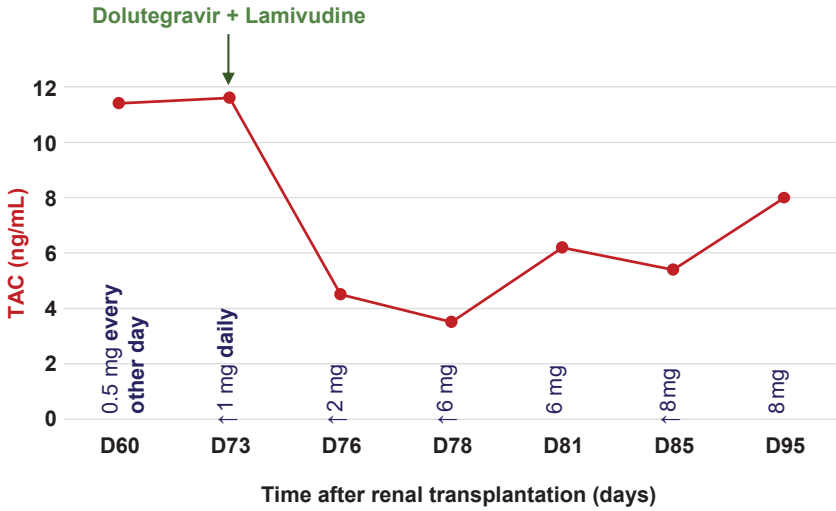

Fig. 4. Trough blood concentration of tacrolimus after changing antiretroviral treatment.

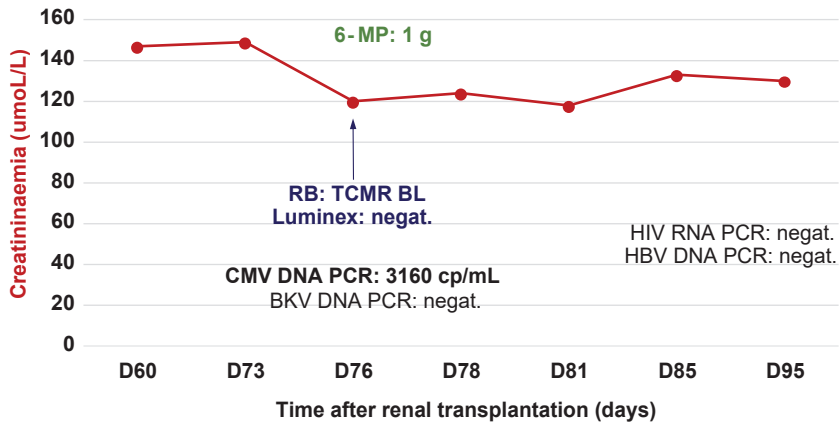

Fig. 5. The course of graft function after changing antiretroviral treatment.

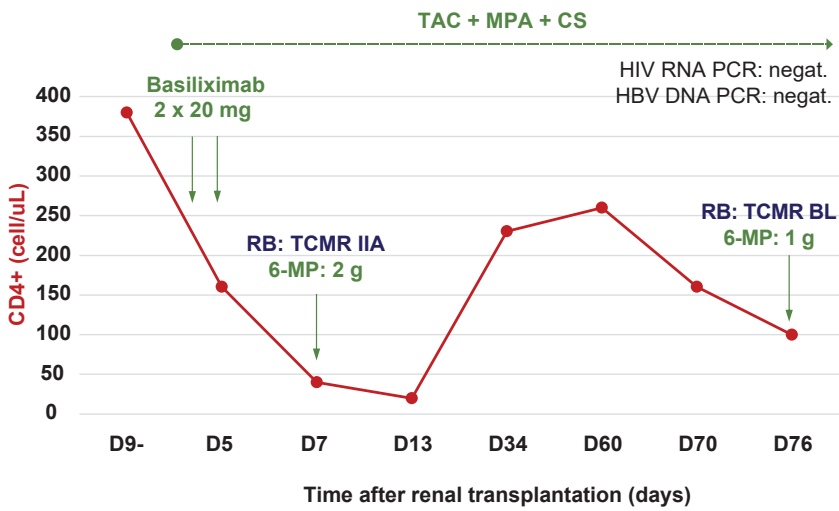

Fig. 6. The course of CD4⁺ according to immunosuppressive treatment.

had stable HIV disease and was on HAART regimen for >3 years before transplantation, his HIV RNA was undetectable in last 3 years and CD4⁺ T lymphocytes counts improved rapidly after HAART initiation. Although the opportunistic infection of hepatitis B was revealed, HBV DNA testing before transplantation was negative. In absence of kidney biopsy, the most probable cause of CKD was HIVAN as evident by rapid progression of kidney disease to end stage renal disease.

The case of the first ever kidney transplantation in an HIV positive patient in Slovakia is used to present the peculiarities of preparation, inclusion criteria, post-transplantation course, monitoring, complications related to drug interaction. In addition to the generally applicable conditions, specific criteria must be met for patient acceptance into the transplantation program, in particular undetectable HIV viral load, stable ARV regimen and CD4⁺ T lymphocyte count higher than 200/uL of blood at least 6 months prior to transplantation, which specified that patients must have an undetectable viral load and a CD4⁺ T lymphocytes count of >200 cells/uL on a stable antiretroviral therapy (ART) regimen for at least six months (12).

Given the higher incidence of co-infections in HIV positive patients, targeted testing for hepatitis B, hepatitis C and tuberculosis in particular is recommended (4). In the case of hepatitis B, as in our case report, HBsAg testing was not sufficient. In a patient with seroconversion, only anti-HBc total testing revealed overcoming hepatitis B.

In agreement with other authors (18, 19, 20, 21), we observed a rapid rise in trough concentration of tacrolimus due to strong drug-drug interactions with protease inhibitors (darunavir and ritonavir). The high TAC concentration accompanied by deterioration of graft function and a decrease in diuresis necessitated several days of treatment interruption and, in fear of activation of HIV and HBV viruses, warranted a single administration of rifampicin, which is one of the potent inducers of some cytochrome P450 enzymes, thereby altering the metabolism of many drugs that are metabolized by these enzymes. Rifampicin, through induction including CYP3A4, accelerates

tacrolimus metabolism (34). The use of cytochrome P450 inducers in patients with toxic CNI concentrations due to drug-drug interactions may be an effective preventive measure to avoid toxicity to life-threatening complications in patients treated with antiviral therapy (35). However, based on our own experience, we recommend that a change in ARV therapy should be consulted before transplantation. Appropriate HAART in patients undergoing organ transplantation is based on integrase inhibitor-based regimens. In our case, PIs were replaced with lamivudine after transplantation, resulting in a decrease in tacrolinemia and the need to increase the daily TAC dose.

Additionally, despite the use of more potent immunosuppression, rejection rates exceed those found in HIV-uninfected recipients (36). Higher rejection rates noted in this cohort are in part related to drug-drug interactions between the anti-retroviral and immunosuppressive regimens, and these interactions can be minimized by switching potential recipients to integrase inhibitor-based regimens prior to transplant if deemed safe by a HIV provider (4). Renal biopsy and treatment according to histological finding is crucial.

Regular monitoring of the HIV viral load and $CD4^+$ count is recommended after kidney transplantation at one month and then every three months posttransplant; this is particularly important if the ART was modified in the period after the transplantation (35).

Conclusion

Kidney transplantation has become the standard of care for patients with HIV and end-stage kidney disease. HIV positive patients encounter very specific issues after transplantation, specifically related to drug interactions and higher rejection rates. Despite that, HIV positive patients have similar results to HIV negative patients post transplantation (4). HIV positive CKD patients with stable disease should not be denied the benefit of kidney transplantation as patient and graft survival is reasonably good, and when monitored closely, the chances of progression of the HIV disease are minimal (37). Kidney transplantation is now accepted as "standard of care" for HIV positive patients with ESKD.

The change in legislation in Slovakia has made it possible to broaden the spectrum of patients accepted into the transplantation program (29).

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