

HIV and kidney transplantation in Romania: The index case

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Abstract

Introduction: Human immunodeficiency virus (HIV) is no longer considered a contraindication for kidney transplantation (KT). KT management in HIV patients is a complex process with challenges, such as drug interactions between immunosuppression and antiretroviral (ARV) therapy. In our country, no KT has been performed thus far in this category of patients.

Case presentation: We present the case of a 29-year-old female patient with HIV and end-stage renal disease (ESRD) who performed a KT from a related living donor in March 2022. KT immediate evolution was favorable. No transplant-related complications were reported. HIV viral load remained undetectable and CD4+ T cells were constantly > 500 cell/ μ L, during the 18 months of follow-up. The main challenge in our case was the drug interaction between the protease inhibitor-based regimen and tacrolimus. This led to tacrolimus overdose, and, subsequently, change in ARV therapy. ARV switching was performed on a regimen based on integrase inhibitor and nucleoside reverse transcriptase inhibitors. After the ARV change, the therapeutic level of tacrolimus was easily reached and maintained. Kidney graft function remained normal during follow-up, despite tacrolimus overexposure, and no rejection or anti-HLA antibodies were observed. Another challenge was related to the donor's hepatitis C virus status (positive antibodies, negative nucleic acid test). The recipient did not develop seroconversion or detectable viremia at 3-, 6-, 12- and 18-months post-KT.

Conclusion: We reported the first case of a successful KT in an ESRD patient with HIV in Romania, in whom the post-transplant evolution was favorable.

Key words: HIV, kidney transplantation, Romania, immunosuppression, drug, interaction.

What is new? What is important?

This is the report of the first case of a kidney transplant performed in a patient with end-stage renal disease and HIV in Romania. In these patients, the interaction between protease inhibitors and tacrolimus causes tacrolimus overdose and increases its toxicity. Tacrolimus levels should be checked very frequently and a decision to switch to an antiretroviral regimen without protease inhibitors is important and should be considered. Also, the use of a kidney graft from a donor with positive serology for hepatitis C virus only requires informing the recipient regarding the minimal but existing risk of developing the infection and the requirement for a strict monitoring of viremia.

INTRODUCTION

According to the Joint United Nations Program on Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS), there were 38.4 million people living with HIV and 1.5

million became newly infected with HIV in 2021, worldwide [1]. In Romania, the cumulative incidence of HIV between 1985 and 2022 was 26,554 cases, out of which 17,664 were AIDS [2]. Chronic kidney disease (CKD) is one of the most important complications in patients with HIV. Its prevalence

varies between 3.5% and 48.5% according to the study design, studied population and CKD definition [3–5]. Although the incidence of end-stage renal disease (ESRD) caused by HIV-associated nephropathy follows a downward trend due to more effective antiretroviral (ARV) therapy, that attributed to diabetes and hypertension is increasing [6,7]. The spectrum of biopsy-proven kidney disease in the modern era is mainly related to diabetic nephropathy, tubulointerstitial disease due to ARV toxicity, HIV-associated nephropathy and immune complex mediated kidney diseases [8]. HIV-associated nephropathy is involved in a small percentage of CKD cases, but is commonly observed in patients with acute kidney injury [8].

Previously, KT was considered a contraindication in HIV-positive patients with ESRD. Currently, it represents the optimal renal replacement therapy method for this category of patients, due to the long-term survival benefit compared to chronic dialysis [9]. Nevertheless, these patients may still face barriers in the evaluation and listing processes [10]. HIV-positive candidates have a decreased probability for waiting list enrollment and access to KT compared to HIV-negative candidates [11]. Among the most common reasons for non-eligibility are drug abuse, failure to complete transplant work-up and uncontrolled HIV [10]. Psychosocial factors, general health issues, cardiovascular condition and persistent reluctance of healthcare providers linked to fear of a complicated outcome are also potential reasons for limited access to KT [11]. Patient survival is significantly increased in the first 5 years after-KT when using a kidney graft from a living donor, but these patients have a 47% more decreased likelihood of receiving such a graft compared to HIV-negative candidates [12]. KT in HIV-positive patients remains a complex process, which involves the fulfilment of general and HIV-specific eligibility criteria, and implies challenges related to the rejection risk, infectious risk and drug interactions between immunosuppression and ART [13].

In Romania, data regarding CKD, including KT, in HIV-positive patients are lacking and up to this date, no other KT was performed in this category of patients. The purpose of this article is to report the first case of a KT in a HIV-positive

ESRD patient in Romania, to highlight the challenges encountered in the management of this case and to show the short-term evolution and outcome.

CASE PRESENTATION

PATIENT PRESENTATION AND INITIAL WORK-UP

We present the case of a 29-year-old female living with HIV and ESRD due to an antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, who performed a KT from a related living donor in March 2022. She was diagnosed with HIV in 2012, transmitted through sexual contact, with undetectable viremia and constant CD4+ lymphocytes count > 200 cells/ μ L since 2015 and no history of opportunistic infections. Before the KT she performed 11 months of hemodialysis. Previously, the patient was on multiple ARV regimens to which she was compliant. At the moment of KT, the regimen included raltegravir (RAL) 800 mg/day, darunavir (DRV) 800 mg/day and ritonavir (RTV) 100 mg/day (Figure 1). Recipient eligibility criteria and lab tests at the time of KT are shown in Table 1 and Table 2. The donor was a 50-year-old male (her father) with a 5-year history of controlled hypertension, a positive hepatitis C virus (HCV) serology (HCV antibodies), but undetectable HCV RNA. Regarding transplant features, the donor-recipient HLA compatibility was 50%, with a living kidney donor profile index score of 48 points, a cold ischemia time of 140 minutes and a warm ischemia time of 28 minutes. Induction immunosuppression consisted of Basiliximab 20 mg administered intravenous (Day 0 and Day 4) and intravenous methylprednisolone (500 mg – day 0, 500 mg – day 1, 250 mg – day 2, 125 mg – day 3). Maintenance immunosuppression was based on extended-release tacrolimus (ER-TAC) initiated 7 days before KT in a particular manner, thereafter, adjusted according to tacrolimus level target, mycophenolate sodium 720 mg twice daily started on day 0 and 20 mg prednisone started on day 4, tapered by 5 mg/week after the first month down to 5 mg/day (Figure 1). Antibacterial, antifungal, and antiviral prophylaxis were performed according to the center's protocol.

CASE EVOLUTION AND MANAGEMENT

KT immediate evolution was favorable. No transplant-related complications (infectious, rejection, urological, vascular) were reported. HIV viral load remained undetectable, CD4⁺ T cells were constantly >500 cell/ μ L and the patient did not develop opportunistic infections, including cytomegalovirus and BK virus infections. No anti-HLA specific antibodies were identified during follow-up, HCV viremia evaluated at constant intervals was undetectable and HCV antibodies remained negative.

Details regarding immunosuppressive therapy, tacrolimus levels and ARV regimens are depicted in Figure 1. In the first 35 days after KT, the ARV consisted of RAL, DRV and RTV. In the week before KT, the initial dose of ER-TAC was 0.5 mg/day, then 1 mg/day and 1 mg every 48 h to achieve a target tacrolimus level of 10 ng/mL at the time of transplantation. In the first 2 days after KT the tacrolimus level dropped nearly to 0 ng/mL, requiring an increase in the ER-TAC dose frequency to 1 mg/day for 7 days until the target level was reached. On day 7, ER-TAC was not administered, then on day 8 the patient received a dose of 0.5 mg/day. After these changes, an overdose of tacrolimus occurred between days 12–18, with values ranging from 21.8 ng/mL to 26.4 ng/mL, during which ER-TAC was stopped. ER-TAC administration was resumed on day 19 with 0.5 mg/day, but another overdose of tacrolimus (17.2 ng/mL) recurred, so it was stopped until day 28, when tacrolimus levels returned to the therapeutic target and a dose of 0.5 mg/day was administered. On day 28, the dose of mycophenolate sodium was decreased to 540 mg twice daily according to the level of serum mycophenolic acid. Tacrolimus level remained in the therapeutic window between days 28–35 after KT. Given the difficulty in obtaining optimal tacrolimus levels, due to drug interactions between protease inhibitors (PI) and ER-TAC, an infectious disease service evaluation was requested for ARV switch. Following the evaluation, the ARV regimen was changed to dolutegravir (DTG) 50 mg/lamivudine (3TC) 300 mg/day. This ART regimen was maintained between days 36–57 and was subsequently changed to DTG 50 mg/day and emtricitabine (FTC) 200 mg/tenofovir alafenamide (TAF) 25 mg/day. After switching to DTG 50 mg/3TC 300 mg/day, the ER-TAC dose was modified to 0.15 mg/kg/day to achieve the target tacrolimus level. Also, after this switch, no significant under- or overdosage of tacrolimus was observed during follow-up.

A further decrease of mycophenolate sodium to 360 mg twice daily was performed at 2 months post-KT. From day 2 post-KT throughout the 18-month follow-up, the kidney graft function, based on serum creatinine, was in the normal range and no urine abnormalities were observed.

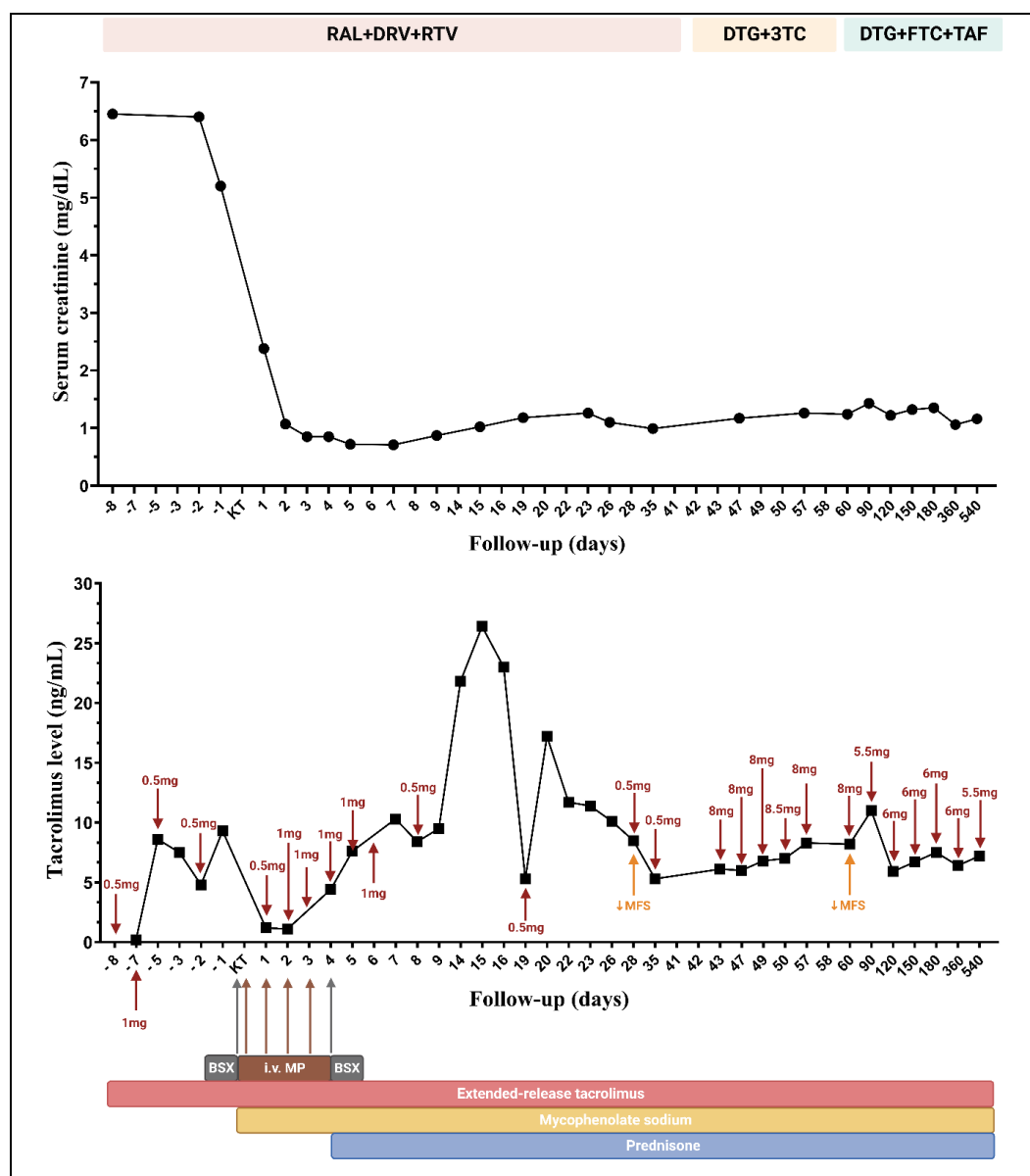
DISCUSSION

Data regarding CKD in HIV patients from Romania, including ESRD and dialysis, are lacking. In our country, no KT had been performed so far in this category of patients. This is the first case of a KT in a patient with HIV and ESRD. KT is the optimal method of renal replacement therapy, being associated with a significant improvement in survival and quality of life compared to patients on dialysis [9]. In terms of donor type, our patient received a kidney graft from a living related donor. Living donors are less frequently seen than deceased donors in this category of patients, but offers by far a better graft survival rate [9,12]. Regarding immunosuppressive treatment, we used an IL2 receptor antagonist and methylprednisolone for induction and classical triple therapy with tacrolimus, mycophenolate, and prednisone for maintenance, according to current recommendations in patients living with HIV [14].

The main challenge in our case was the drug interaction between the PI-based ARV regimen and tacrolimus. RTV is a potent inhibitor of cytochrome P450 (CYP) 3A4/5 and P-glycoprotein. Tacrolimus is mainly metabolized by both CYP3A4 and CYP3A5 and is a substrate for P-glycoprotein. Coadministration of the two drugs decreases the rate of tacrolimus metabolism and leads to tacrolimus overdose, which predisposes to toxicity [15]. Although ER-TAC initiation was performed one week prior to KT according to the Erik M. van Maarseveen *et al.* model, in order to obtain a favorable pharmacokinetic curve at the time and after transplantation, we encountered difficulties in handling tacrolimus [16]. Overexposure was the main concern that led to changing the ARV regimen. The change of ARV in the post-transplant setting was a particularity. Current guidelines recommend that ARV changes should be made at least 6 months prior to KT, but do not give details regarding the post-transplant approach. In our case, two successful ARV regimen changes were achieved post-transplantation. Initially, we switched to a combination of an integrase inhibitor (II) and a nucleoside reverse transcriptase inhibitor (NRTI)

and then to a combination of an II and two NRTIs. The strategy of changing ARV regimen to one without PIs should always be considered, given that PIs determines high inpatient tacrolimus variability, decreased graft function and a significantly higher rate of short-term rejection [17,18]. We did not experience degradation of kidney graft function, despite tacrolimus overexposure, rejection or development of anti-HLA antibodies. After the discontinuation of PIs, the therapeutic window of tacrolimus, between 6-8 ng/mL was easily reached and maintained. There are different experiences

with changing ARV regimen based on one II and two NRTIs after KT. Humberto Jimenez *et al.* observed that switching from a ritonavir-based regimen to DTG/FTC/TAF at 6 months after KT led to subtherapeutic tacrolimus concentrations and an increased serum creatinine. In another case report, Jennifer Lagoutte-Renosi *et al.* showed that the change of RAL/ETR/DRV/RTV regimen with BIC/FTC/TAF at day 20 after KT, was associated with tacrolimus overdosage. The authors' explanation was related to the fact that tacrolimus was re-introduced too early after discontinuation of RTV.



Another challenge of the case was related to the donor's HCV status (HCV-seropositive antibodies, HCV nucleic acid testing negative). This scenario can result in a 44% rate of seroconversion and a 1.9% risk of HCV transmission in the recipient [19,20]. In our case, the recipient did not develop seroconversion or detectable viremia at 1, 3-, 6-, 12- and 18-months post-KT. In case of detectable viremia, the patient would have required interferon-free anti-HCV treatment which could have been a real challenge due to drug interactions with ARVs and immunosuppression.

Performing a KT in a patient living with HIV is complex and challenging, often with a fine line between risks and benefits, but offers superior quality of life and survival. This case has opened the barriers to solid organ transplantation in HIV patients in Romania. In the absence of epidemiological data, we cannot estimate how many patients with HIV infection would need KT at this moment. However, as the incidence of ESRD among these patients is increasing worldwide, we can anticipate that this will also happen in our country. Estimating the burden of CKD in HIV-positive patients is important when considering the allocation of resources including dialysis, availability of deceased and living donor organs, and transplantation. Current guidelines, the evolution

and understanding of immunosuppression as well as the availability of ARV medication are key elements in achieving and perfecting the KT process in this category of patients. However, in order to improve and increase the number of transplants for patients with HIV infection, regular training of the medical staff involved would be necessary. Successful kidney transplantation in HIV-positive patients requires comprehensive patient evaluation, careful patient selection, comprehensive medical management, judicious management of immunosuppression, understanding of infectious, malignancy, cardiometabolic risks, and ongoing collaboration among various healthcare professionals. In our patient's case, a multidisciplinary collaboration between nephrologist, urologist, anesthesiologist, immunologist, infectious disease specialist, cardiologist and primary care physician was necessary to perform the KT.

CONCLUSION

We reported the first case of a KT in an ESRD patient with HIV in Romania, in whom the post-transplant evolution was favorable with undetectable viremia, without surgical, infectious or immunological complications and with normal kidney graft function.

Introducere: Infecția cu virusul imunodeficienței umane (HIV) nu mai reprezintă o contraindicație pentru transplantul renal (TR). TR la pacienții HIV pozitivi este un proces complex și provocator, una dintre cele mai frecvente provocări fiind managementul interacțiunilor medicamentoase între medicația antiretrovirală (ARV) și tratamentul imunosupresor. În România nu a fost realizat niciun transplant renal la această categorie de pacienți, până la acest moment.

Prezentarea cazului: Prezentăm cazul unei paciente în vârstă de 29 de ani, cunoscută cu infecție HIV și boală cronică de rinichi în stadiul final (ESRD) care a beneficiat de un TR de la donator viu înrudit în martie 2022. Nu au fost raportate complicații asociate transplantului. Viremia HIV a rămas nedetectabilă și nivelul limfocitelor CD4 a fost constant > 500 celule/ μ L pe parcursul celor 18 luni de urmărire. Principala provocare a cazului a fost reprezentată de interacțiunea medicamentoasă între regimul ARV bazat pe inhibitori de protează și tacrolimus. Această interacțiune a determinat supradozarea tacrolimusului și a condus la schimbarea regimului ARV. Modificarea regimului ARV a constat în trecerea pe o combinație între inhibitori de integrază și inhibitori nucleozidici de reverstranscriptază. În urma modificării, nivelul terapeutic al tacrolimusului a fost atins și menținut cu ușurință. Funcția grefei renale a rămas în permanență în limite normale, în ciuda supradozărilor tacrolinemiei, și pacienta nu a dezvoltat rejet sau anticorpi anti-HLA. O altă provocare a cazului a ținut de statusul donatorului privind virusul hepatitic C (anticorpi prezenți, viremie nedetectabilă). După transplant, în cazul receptorului, nu s-a observat seroconversie sau viremie detectabilă la 3, 6, 12 și 18 luni.

Concluzie: Am raportat primul caz de TR la un pacient cu ESRD și infecție HIV din România, a cărui evoluție post-transplant a fost favorabilă.

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