


# The first report of kidney transplantation in a human immunodeficiency virus–positive recipient in Thailand and literature review: Encouragement for developing countries in Southeast Asia

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Suwasin Udomkarnjananun<sup>1,2,3</sup> , Nuanjanthip Naiyaraksee<sup>1</sup>, Natavudh Townamchai<sup>1,2,3</sup>, Ekkapong Surinrat<sup>1</sup>, Kanitha Tiankanon<sup>1</sup>, Athiphat Banjongjit<sup>1</sup>, Jakapat Vanichanan<sup>4</sup>, Kamonwan Jutivorakool<sup>4</sup>, Opass Putcharoen<sup>4</sup>, Chusana Suankratay<sup>4</sup>, Jerasit Surintrspanont<sup>5</sup>, Kroonpong lampenkhae<sup>5</sup>, Asada Leelahavanichkul<sup>6</sup>, Salin Wattanatorn<sup>1,3</sup>, Kirada Apisitumaitri<sup>3,7</sup>, Rattanaporn Burimsittichai<sup>3,7</sup>, Supoj Ratchanon<sup>8</sup>, Bunthoon Nonthasoot<sup>3,8</sup>, Boonchoo Sirichindakul<sup>3,8</sup>, Kearkiat Praditpornsilpa<sup>1</sup> and Yingyos Avihingsanon<sup>1,2,3</sup>

## Abstract

Patients with human immunodeficiency virus infection are at risk of chronic kidney disease and end-stage renal disease. Human immunodeficiency virus infection impedes patients' accessibility to transplantation in Thailand and other developing countries in Southeast Asia, where the burdens of human immunodeficiency virus infection and chronic kidney disease are rapidly increasing. We report the successful kidney transplantation in a human immunodeficiency virus–positive recipient in Thailand and provide brief information about the current knowledge of human immunodeficiency virus medicine and transplantation that are needed for conducting kidney transplantations in such patients. Patient selection and evaluation, the choice of antiretroviral therapy, immunosuppressive regimens, and infectious complications are reviewed and discussed. The aim is to encourage kidney transplantation in end-stage renal disease patients with well-controlled human immunodeficiency virus infection, especially in countries where the prevalence of human immunodeficiency virus infection is high and the accessibility to transplantation is still limited.

## Keywords

Kidney transplantation, immunosuppression, human immunodeficiency virus, end-stage renal disease

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<sup>1</sup>Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

<sup>2</sup>Renal Immunology and Transplantation Research Unit, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

<sup>3</sup>Excellence Center for Solid Organ Transplantation, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

<sup>4</sup>Division of Infectious Disease, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

<sup>5</sup>Department of Pathology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

<sup>6</sup>Department of Microbiology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

<sup>7</sup>Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

<sup>8</sup>Department of Surgery, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

## Corresponding Author:

Suwasin Udomkarnjananun, Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, 1873, Rama 4 Road, Bangkok 10330, Thailand.

Email: suwasin.u@gmail.com



## Introduction

The prevalence of human immunodeficiency virus (HIV) infection is high in Southeast Asia (SEA). Indonesia, Thailand, and Myanmar are the countries in the region with the top-three highest burdens, with a cumulative total of 1.4 million HIV patients according to the World Health Organization (WHO).<sup>1</sup> Patients with HIV infection are at risk for chronic kidney disease (CKD) and end-stage renal disease (ESRD) due to several mechanisms, including the HIV itself, antiretroviral therapy (ART)-related nephrotoxicity, opportunistic infections, and the metabolic complications related to HIV infection.<sup>2</sup>

In SEA region, it is estimated that around 7000 ESRD patients have HIV co-infection considered that 0.5% of HIV patients develop ESRD.<sup>3</sup> HIV patients in Thailand who progress to ESRD receive either peritoneal dialysis or hemodialysis, and do not have access to kidney transplantation.<sup>4</sup> We report the first kidney transplantation in an HIV-positive recipient in Thailand and encourage accessibility to kidney transplantation for this group of patients.

## Case presentation

A 33-year-old male with HIV infection received a kidney transplantation from his 30-year-old sister. The patient had been infected with HIV 13 years prior by his partner. He had complete treatment for secondary syphilis and tuberculous lymphadenitis 10 years prior. He developed CKD, which was suspected to have arisen from tenofovir disoproxil fumarate (TDF) and eventually progressed to ESRD. The patient had received peritoneal dialysis during the last 1 year before transplantation. Hepatitis C virus (HCV) antibody was negative. The patient had completed the hepatitis B virus (HBV) immunization with a pretransplant hepatitis B surface antibody (anti-HBs) >100 IU/L.

The patient's blood pressure, physical examination, and laboratory results were within normal limits during follow-up. His pretransplantation ART comprised abacavir at 300 mg/day, lamivudine at 150 mg/day, and nevirapine at 200 mg/day, which were able to control his HIV viral load to <20 copies/mL and his CD4+ T lymphocytes to 604 cells/ $\mu$ L before transplantation. The serology results for HBV and HCV were all negative. The cytomegalovirus (CMV) serology result was positive for both the donor and recipient. The patient's human leukocyte antigen (HLA) mismatch was 0/6 with a compatible blood group. The pretransplantation complement-dependent cytotoxicity (CDC) crossmatch result was negative.

Antithymocyte globulin (ATG) was given as an induction therapy due to the high rate of acute rejection in HIV-positive kidney transplantation<sup>5-7</sup> and in consideration that young recipients have lower risk for posttransplant infectious complications.<sup>8</sup> CD4+ and lymphocyte counts were closely monitored in the first week after transplantation, and the total dose of ATG was adjusted to 2.5 mg/kg. One gram

of intravenous ceftriaxone was used as the prophylactic antibiotic immediately after transplantation and followed by cotrimoxazole (160 mg of trimethoprim and 800 mg of sulfamethoxazole daily). The maintenance regimen included tacrolimus (target trough concentration 7–8 ng/mL), mycophenolate mofetil (starting at 1500 mg/day and decreased to 1000 mg/day after 1 week), and prednisolone (starting from 60 mg/day and then tapered to 5 mg/day within 4 months).

The patient's posttransplant clinical course is shown in Table 1. His CD4+ lymphocyte count decreased to 10 cells/ $\mu$ L in the first week and slowly recovered to >200 cells/ $\mu$ L within 6 weeks. Few posttransplantation complications occurred, including perinephric collection, which was treated conservatively, and CMV viremia detected by preemptive surveillance, which necessitated a 1-month course of ganciclovir. Monthly BK virus screenings were negative for BK viremia. The patient is doing well and has had stable graft function as of 6 months posttransplantation.

## Discussion

The outcomes of kidney transplantation in HIV-positive ESRD patients are better than those of dialysis, particularly in terms of patient survival.<sup>9</sup> Evidences have shown that the allograft and patient survival rates are comparable between the HIV-monoinfected and the HIV-negative kidney transplant recipients.<sup>10-12</sup> However, some studies demonstrated that the HIV-positive recipients had inferior long-term patient survival compared with the HIV-negative.<sup>5,13</sup> The difference in survival among these studies could be explained from the changing era of immunosuppression, the different ART used, and the HCV co-infection. Patients with HCV co-infection are at risk for inferior allograft and patient survival compared with the HIV-monoinfected and HIV-negative recipients.<sup>10,12</sup> In the upcoming decade, it is possible that there will be further improvement in the outcomes of HIV-positive kidney transplantation due to the widespread use of tacrolimus-based regimen (compared to cyclosporine in the previous era), the more accessible integrase inhibitors, and the use of direct-acting antivirals (DAAs) for the treatment of HCV co-infection. The following discussion includes a brief summary of distinctive considerations for HIV-positive kidney transplantation (Table 2).

### Patient selection and evaluation

The standard criteria for HIV-negative kidney transplantation can be applied, which include an absence of active infection or malignancy. HIV patients are at higher risk of cardiovascular diseases as a consequence of HIV-associated immune activation and inflammation, as well as ART-related adverse effects.<sup>14</sup> Pretransplant evaluation should incorporate screening for hidden cardiovascular comorbidities, including electrocardiography and peripheral pulse examination.

**Table 1.** Posttransplantation clinical course.

Parameters	D0 (transplant date)	D1	D7	D15	D30	D45	D120
Serum creatinine (mg/dL)	16.7	3.5	1.0	1.3	1.1	1.3	1.5
Proteinuria (mg/day)	–	833	55	<30	<30	<30	<30
Tacrolimus (trough concentration, ng/mL)	–	12.8	6.7	7.6	5.1	7.0	9.2
CD4+ T lymphocyte (cells/ $\mu$ L)	604	–	10	46	–	217	237
HIV viral load (copies/mL)	<20	–	<20	–	<20	–	<20
CMV viral load (copies/mL)	–	–	<20	32	1784 (started ganciclovir)	<20	<20

HIV: human immunodeficiency virus; CMV: cytomegalovirus.

**Table 2.** Summary of recommendations in HIV-positive kidney transplantation recipients.

Considerations	Recommendations
Patient selection	<ul style="list-style-type: none"> <li>– Meet standard criteria for kidney transplantation</li> <li>– No active infection or malignancy</li> <li>– Stable ART regimen for at least 3 to 6 months with undetectable HIV viral load and CD4+ lymphocyte count &gt;200 cells/<math>\mu</math>L</li> <li>– No chronic debilitating diseases: chronic intestinal cryptosporidiosis, PML, and primary CNS lymphoma</li> </ul>
ART regimen	<ul style="list-style-type: none"> <li>– Prefer integrase inhibitor–based regimen</li> <li>– Avoid PI-based regimen</li> </ul>
Induction regimen	<ul style="list-style-type: none"> <li>– ATG has more evidence for preventing rejection than others</li> <li>– Should be determined based on immunological risk, infectious risk, pretransplant CD4+ lymphocyte count, comorbidities, and the patient's frailty</li> </ul>
Maintenance regimen	<ul style="list-style-type: none"> <li>– Tacrolimus, mycophenolate, and corticosteroid are standard</li> <li>– CSA and sirolimus increase the risk of acute rejection compared with tacrolimus</li> <li>– Early steroid withdrawal increases the risk of acute rejection</li> </ul>
Infection prophylaxis	<ul style="list-style-type: none"> <li>– Cotrimoxazole prophylaxis is used for bacterial urinary tract infection, toxoplasmosis, and pneumocystis pneumonia</li> <li>– Acyclovir prophylaxis is used for HSV and VZV</li> <li>– CMV prophylaxis is preferred than preemptive strategy</li> <li>– Prophylaxis for other opportunistic infections is considered regarding the posttransplant CD4+ lymphocyte count and endemic area</li> <li>– BK virus monitoring same as HIV-negative recipients</li> </ul>
Malignancy screening	<ul style="list-style-type: none"> <li>– Age-related recommendation screening protocols for colorectal, cervical, breast, lung, and prostate cancer</li> <li>– Yearly imaging of the native kidneys</li> </ul>

HIV: human immunodeficiency virus; ART: antiretroviral therapy; PML: progressive multifocal leukoencephalopathy; CNS: central nervous system; PI: protease inhibitor; ATG: antithymocyte globulin; CSA: cyclosporin A; HSV: herpes simplex virus; VZV: varicella-zoster virus; CMV: cytomegalovirus.

In regard to the HIV infection, recipients should have an undetectable HIV viral load and a CD4+ lymphocyte count >200 cells/ $\mu$ L with a stable unchanged ART regimen for at least 3 to 6 months. Kidney transplantation is contraindicated for patients who have opportunistic infections or neoplasm without effective eradication strategy, including progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, and primary central nervous system lymphoma.<sup>15</sup> Regarding ART, an integrase inhibitor–based regimen is preferred since integrase inhibitors are not a substrate for cytochrome P450 (CYP). In contrast, protease inhibitors (PIs) and cobicistat are strong CYP3A4 inhibitors and significantly increase the concentrations of calcineurin

inhibitor (CNI) and mammalian target of rapamycin inhibitor (mTORi).

If the standard trough concentrations of CNI and mTORi are used in patients receiving PIs, a marked increase in dosing interval or a reduction in dosage is necessary, and they might contribute to insufficient immunosuppression or toxicities.<sup>16,17</sup> Moreover, PI-based ART significantly increases the risk of allograft loss and death in comparison with a non-PI-based regimen.<sup>18</sup> Patients who receive non-nucleotide reverse transcriptase inhibitors (NNRTIs) may require an increase in CNI and mTORi dosages since NNRTIs are a CYP inducer, but with less effect than PIs.<sup>19</sup> Therefore, HIV-positive recipients should

avoid PI-based ART and should switch to an integrase inhibitor-based regimen or to NNRTIs if the integrase inhibitors are not available in some countries.

### *Immunosuppression and rejection*

Kidney transplantation recipients with HIV infection are at higher risk of acute rejection than HIV-negative recipients (the risks are approximately 30% and 10% in the first year after transplantation, respectively).<sup>5,6,11</sup> There are many hypotheses regarding the high rejection rate, including HIV containing HLA molecules, the memory phenotype of T lymphocytes in HIV-positive patients, HIV-associated immune dysregulation, and cross-reactivity between the virus and donor antigens.<sup>20–22</sup> However, there is growing interest in the drug interactions between ART, especially PIs and CNIs or mTORi. This results in a reduction of the area under the concentration–time curve (AUC) of the immunosuppressive medications when the dosing intervals have to be increased in order to achieve the same trough concentration. This might predispose patients to allograft rejection.<sup>17,18</sup>

Regarding the induction regimen, ATG has more evidence for preventing rejection in HIV-positive kidney transplantation than interleukin-2 (IL-2) receptor antagonists.<sup>7,23,24</sup> In addition, patients who have not received any induction have the highest risk for death and allograft loss.<sup>23</sup> However, the induction regimen should also be based on the immunological risk, infectious risk, pretransplantation CD4+ lymphocyte count, comorbidities, and the patient's frailty. A pretransplantation CD4+ lymphocyte count of less than 350 cells/ $\mu$ L is a risk factor for developing CD4+ lymphopenia after transplantation in patients receiving ATG, which increases the probability of the patient contracting serious infections thereafter.<sup>25</sup>

The standard maintenance regimen is recommended for HIV-positive kidney transplantation recipients, including tacrolimus, mycophenolate, and corticosteroid. Cyclosporine A and sirolimus are inferior to tacrolimus in the prevention of acute rejection.<sup>7,26</sup> The dose of mycophenolate should be adjusted according to the total and CD4+ lymphocyte count. Recent evidence from HIV-positive recipients has shown that early corticosteroid withdrawal before hospital discharge is an independent risk factor for acute rejection at 1-year posttransplantation, but there is no difference in graft or patient survival.<sup>27</sup>

### *Infection prophylaxis, malignancy screening, and other considerations*

Posttransplantation infection prophylaxis in HIV-positive recipients is not different from that used for HIV-negative patients. Cotrimoxazole is generally used as a prophylaxis for bacterial urinary tract infection in kidney transplant recipients and is also beneficial in preventing pneumocystis pneumonia and toxoplasmosis in HIV-positive patients, particularly those receiving ATG who suffer from CD4+ lymphopenia.

The recommended cotrimoxazole dosage is 80 to 160 mg of trimethoprim and 400 to 800 mg of sulfamethoxazole per day, with a minimum of 12 months after transplantation.<sup>28</sup> The optimal duration for this prophylaxis is still unknown but often extended to lifelong in some transplant centers since there are cases of pneumocystis pneumonia even after 1-year posttransplantation.<sup>13,29</sup> Acyclovir is recommended for the prophylaxis of herpes simplex virus and varicella-zoster virus. For CMV prevention, prophylactic therapy is more preferred than a preemptive strategy in HIV-positive transplantation.<sup>30</sup> The recommended regimen is 900 mg of valganciclovir with a minimum of 3 months duration and should be extended to 6 months in the CMV seronegative recipients who received the allograft from CMV seropositive donors. In patients who receive the antirejection treatment, these prophylactic strategies should be resumed if already been stopped.

Prophylaxis against other infectious diseases depends on the transplant center and whether the patients live in an endemic area or not. The incidence of infectious complications after transplantation seems to be similar to that of HIV-negative patients.<sup>31</sup> Malignancy-screening protocols are not different from the age-related recommendations for general kidney transplant recipients, including colorectal, cervical, lung, breast, prostate, and renal cancer. The incidence of Kaposi's sarcoma is higher in HIV-positive organ transplantation recipients than those who are HIV-negative, but they respond well to treatment with mTORi.<sup>32</sup>

Recurrence or de novo HIV-associated nephropathy (HIVAN) is a concern in HIV-positive kidney transplantation recipients with African ancestry who carry the *APOL1* G1 and G2 alleles. However, these high-risk alleles are not found in those with Asian ancestry,<sup>33</sup> so the risk of HIVAN in Asian populations is minimal. For patients with allograft failure, the outcomes of retransplantation in HIV-positive patients are poorer than those in HIV-negative patients, and the risk of death and allograft loss is higher.<sup>34</sup>

### *Consideration of HBV/HCV co-infection*

HBV and HCV co-infection are not uncommon in HIV-positive patients and negatively influence the outcomes of kidney transplant recipients.<sup>10,12,35</sup> The treatment of HBV co-infection should be initiated early to prevent the progression of hepatitis and liver fibrosis. Patients with HBV co-infection should receive ART that includes two drugs with activity against HBV such as tenofovir and lamivudine/emtricitabine.<sup>28,36</sup> Tenofovir alafenamide is preferred to TDF due to less nephrotoxicity and bone loss, which are the important complications after transplantation.<sup>36</sup>

The treatment of HCV co-infection has been much improved since the introduction of DAAs. The appropriate timing for HCV treatment, pretransplantation versus posttransplantation, depends on the severity of liver disease and the accessibility to HCV-positive organs.<sup>28,37</sup> ESRD patients with low-grade liver fibrosis in a transplant center that can utilize organs from an HCV-positive donor could decide to

receive the HCV-positive kidney allograft to shorten time in the waiting list. DAAs can then be started after transplantation for the eradication of HCV. On the contrary, pretransplant DAAs treatment is more appropriate for the waitlist patients who already have high-grade liver fibrosis or other HCV-related complications. Patients with decompensated liver cirrhosis should be considered for combined liver–kidney transplantation and deferring HCV treatment after transplantation.<sup>38</sup>

### *The future of HIV-positive transplantation in developing countries and conclusions*

This case presentation is only the early step of organ transplantation in the HIV-positive patients in Thailand. The transplant outcomes would encourage transplant centers in the developing countries to provide transplantation to the patients with HIV-positive, which had been a major barrier to an appropriate care for a long time. Similar to other countries, Thailand is facing the problem of organ shortage and there is an urgent need to increase the donor pool for all solid organ transplantation. Transplantation of the HIV-positive deceased donor to HIV-positive recipients would help maximize the organ utilization and should be considered as the next step for extending the donor pool without interfering the non-HIV donor. Other possible strategies to increase the donor pool include transplantation of HCV-positive deceased donor to the HCV-negative recipients and the protocol for intensive care to facilitate organ donation.<sup>39</sup>

In conclusion, kidney transplantation has become the standard of care for HIV-positive ESRD patients. However, the accessibility to kidney transplantation needs to be improved to serve the increasing number of CKD patients with HIV infection in developing countries in SEA. This study has briefly provided essential information and encourages the establishment of national policy for such patients.

### **Author contributions**

S.U. helped in study design, data collection, and article writing; N.N. helped in study design and data collection; E.S., K.T., A.B., J.V., K.J., O.P., C.S., J.S., K.I., A.L., S.W., K.A., R.B., S.R., B.N., and B.S. contributed to study design; and N.T., K.P., and Y.A. helped in study design and article review.

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### **Ethical approval**

Our institution provided ethical approval for reporting this case according to the consent from patients.

### **Informed consent**

The patient in the presenting case was informed of the study and provided written consent to share his information for academic purposes. The informed consent was signed by the patient and donor.

### **ORCID iD**

Suwasin Udomkarnjananun  <https://orcid.org/0000-0003-4087-9032>

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