



HAL
open science

Kidney transplantation improves the clinical outcomes of Acute Intermittent Porphyria

Hélène Lazareth, Neila Talbi, Nassim Kamar, Charlène Levi, Bruno Moulin, Sophie Caillard, Luc Frimat, Jonathan Maurice M Chemouny, Valérie Châtelet, Clément Vachey, et al.

► **To cite this version:**

Hélène Lazareth, Neila Talbi, Nassim Kamar, Charlène Levi, Bruno Moulin, et al.. Kidney transplantation improves the clinical outcomes of Acute Intermittent Porphyria. *Molecular Genetics and Metabolism*, 2020, 131 (1-2), pp.259-266. 10.1016/j.ymgme.2020.08.004 . hal-02959719

HAL Id: hal-02959719

<https://hal.science/hal-02959719v1>

Submitted on 16 Dec 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Kidney transplantation improves the clinical outcomes of Acute Intermittent Porphyria

Helene Lazareth¹, Neila Talbi², Nassim Kamar³, Charlène Levi⁴, Bruno Moulin⁵, Sophie Caillard⁵, Luc Frimat⁶, Jonathan Chemouny⁷, Valérie Chatelet⁸, Clément Vachey⁹, Renaud Snanoudj¹⁰, Thibaud Lefebvre², Alexandre Karras¹, Laurent Gouya², Caroline Schmitt², Hervé Puy^{2,*}, Nicolas Pallet^{1,11,*}

1. Nephrology Department, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Paris University, France
2. French Porphyria Center, Hôpital Louis Mourier, Assistance Publique-Hôpitaux de Paris, Colombes and Research center on Inflammation, INSERM U1149, Paris University, France.
3. Department of Nephrology, Dialysis and Organ Transplantation, CHU Rangueil, INSERM U1043, IFR-BMT, University Paul Sabatier, Toulouse, France.
4. Department of Transplantation, Nephrology and Clinical Immunology, Edouard Herriot University Hospital, Lyon, France
5. Nephrology and Transplantation Department, University Hospital, Strasbourg, France
6. Nephrology, Dialysis and Transplantation Department, CHU Nancy, Nancy, France
7. Nephrology, Dialysis and Transplantation Department, Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, CIC-P 1414 (Centre d'investigation clinique), F-35000 Rennes, FranceRennes, France
8. Nephrology, Dialysis, Transplantation Department, CHU Cote de Nacre, Caen University, Caen, France.
9. Nephrology, Dialysis and Transplantation Department, CHU Besançon, Besançon, France.
10. Nephrology, Dialysis and Renal Transplantation Department, Hospital Foch, Suresnes, France
11. Clinical chemistry department, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Paris University, Paris, France

* co senior authors

Abstract

Background. Acute Intermittent Porphyria (AIP) is a rare inherited autosomal dominant disorder of heme biosynthesis. Porphyria-associated kidney disease occurs in more than 50% of the patients with AIP, and end stage renal disease (ESRD) can be a devastating complication for AIP patients. The outcomes of AIP patients after kidney transplantation are poorly known.

Methods. We examined the outcomes of 11 individuals with AIP, identified as kidney transplant recipients in the French Porphyria Center Registry.

Results. AIP had been diagnosed on average 19 years before the diagnosis of ESRD except for one patient in whom the diagnosis of AIP had been made 5 years after the initiation of dialysis. Median follow-up after transplantation was 9 years. A patient died 2 months after transplantation from a cardiac arrest and a patient who received a donation after cardiac death experienced a primary non-function. No rejection episode and no noticeable adverse event occurred after transplantation. Serum creatinine was on average 117 $\mu\text{mol/l}$, and proteinuria <0.5 g/l in all patients at last follow up. All usually prescribed drugs after transplantation are authorized except for trimethoprim/sulfamethoxazole. Critically, acute porphyria attacks almost disappeared after kidney transplantation, and skin lesions resolved in all patients.

Conclusion. Kidney transplantation is the treatment of choice for AIP patients with ESRD and dramatically reduces the disease activity.

Key words: Acute intermittent porphyria, kidney transplantation, chronic kidney disease, end-stage renal disease, aminolevulinic acid, porphobilinogen, porphyrin precursors, porphyria cutanea tarda

1. Introduction

Porphyria encompasses a group of eight metabolic disorders of the heme biosynthesis pathway [1, 2]. Acute Intermittent Porphyria (AIP) is an inherited autosomal dominant disorder due to a defect in hydroxymethylbilane synthase (HMBS) [1, 3], the third enzyme of the biosynthetic pathway that catalyzes porphobilinogen (PBG) polymerization into hydroxymethylbilane (**Figure 1**). The estimated prevalence of a symptomatic disease in the Caucasian population is $\sim 1/180\ 000$, and the estimated frequency of clinical pathogenic variants is $\sim 1/1750$ [4, 5]. As AIP is a monogenic disorder, this extremely low penetrance ($\sim 1\%$) suggests a critical role for modifying factors (genetic and/or environmental) in predisposing to symptoms, but also a possible underreporting of the cases due to misdiagnosis. Indeed, AIP is a relatively unknown disease for many physicians. AIP is characterized by the occurrence of acute neurovisceral attacks (abdominal pain, nausea, vomiting, constipation, neurologic or psychiatric symptoms) accompanied by the excretion of large amounts of the porphyrin precursors delta aminolevulinic acid (ALA) and PBG in urine. Whereas the vast majority of AIP patients will experience a limited number of attacks over a lifetime, 3-5% of patients with AIP will have recurrent acute attacks, which can lead to a debilitating medical condition [6].

ALA is a highly hydrophilic molecule that can cross blood barriers, and is freely excreted in the urine. As a potent vasoconstrictor, ALA promotes ischemia and injury in target organs, and, as such, is considered to be directly responsible for the symptoms of AIP [7]. In the liver and kidneys, ALA is produced by ALA synthase 1 (ALAS1), an isoform under the negative control of heme [8] (**Figure 1**). The capacity of a drug or a clinical situation to precipitate acute porphyric attacks, i.e. the “porphyrogenicity”, will depend on its ability to inhibit ALAS1 physiological feedback-control via reduction of the regulatory heme pool within the hepatocyte, for example in inducing P450 cytochromes expression or degradation. Thus, ALAS1 overexpression is a feature of AIP attacks, leading to an increased synthesis of ALA and PBG, and to their systemic accumulation since deficient HMBS cannot fully metabolize PBG into porphyrins.

Porphyrin precursors have a deleterious effect on the kidney. Porphyria-associated kidney disease (PAKD) occurs in more than 50% of the patients with symptomatic AIP. Supporting this, the specific role of ALA and PBG in the chronic renal structural deterioration that accompanies AIP has recently been demonstrated [9]. Two types of renal lesions characterize PAKD: tubular atrophy and interstitial fibrosis associated with non-specific arteriosclerosis, and less frequently, chronic fibrous intimal hyperplasia associated with focal cortical atrophy is observed in the most severe cases [9]. PAKD is not a severe disease in most of the cases, and only a small proportion of patients apparently reach end stage renal disease (ESRD). However, ESRD is a detrimental condition for AIP patients [10], and kidney transplantation

(KTx) can be considered as a therapeutic option. Indeed, case reports suggest that KTx in AIP patients may have a favorable outcome [11-13]. However, critical issues remain unresolved, including the role of the KTx in the activity of the heme biosynthetic pathway, the changes in disease activity after KTx, and the tolerability of several of the medications prescribed to kidney transplant recipients (KTR). To address these issues, we undertook this study to examine the long-term clinical outcomes of a cohort of KTR with AIP in France.

2. Patients and methods

2.1. Study population

The French Porphyria Center (<http://www.porphyrie.net/>) centralizes clinical, genetic and biological information from all AIP patients in France in relationship with caregivers and self reports. For the purpose of this study, a detailed analysis was completed on the subset of patients who developed ESRD and underwent KTx. The data collection period for the number of acute attacks was isometric, that is, centered on the date of the KTx, with same time periods before and after KTx, and dependent on the length of follow-up after KTx.

The institutional review board of Louis Mourier Hospital approved the study, written informed consent was obtained from all patients referenced in the database, and the database has been deposited to the Commission Nationale Informatique et Libertés (CNIL agreement number 1187326).

2.2. AIP diagnosis

The criteria for AIP diagnosis followed the European Porphyria Network guidelines [1, 14]. AIP diagnosis was performed in the French Porphyria Center. Two “AIP status” have been considered. i. The “AIP patient” status is defined by the association of at least one acute porphyric attack (occurrence of abdominal pain, nausea, vomiting, constipation, neurologic or psychiatric symptoms) with a typical porphyrin precursors excretion profile urines. The diagnosis is confirmed by a 50% decrease in HMBS activity in erythrocytes and/or by the identification of a causative mutation in *HMBS* gene by direct sequencing as previously described [15]; ii. The “asymptomatic carrier” status is defined after a family screening to identify those with asymptomatic (or latent) disease and is based on a deficient HMBS enzymatic activity complemented with a DNA analysis by direct sequencing to identify the causative mutation in the *HMBS* gene (which requires prior identification of the mutation in a related affected family member).

2.3. Clinical chemistry

Urinary ALA and PBG were measured using the Bio-Rad ALA/PBG column kit, according to the manufacturer’s protocol and the values were reported to creatinine concentration in urine. Plasma ALA and PBG were measured by Ultra High Pressure chromatography

(Inversed phase chromatography) coupled with a Tandem Mass spectrometer, after protein precipitation and derivatization.

Plasma porphyrins were measured, as already described [16]. Briefly, the plasma in phosphate buffer was compared with a uroporphyrin standard by scanning the fluorescence emission signal from 570 to 750 nm (excitation at 405 nm). Plasma porphyrins were separated by normal-phase high-performance liquid chromatography (HPLC) with fluorimetric detection.

3. Results

3.1. AIP and kidney disease histories

As of March 2020, 1889 individuals (alive or dead, 626 AIP patients and 1263 asymptomatic carriers) were listed in the French Porphyria Center registry. Eleven individuals (10 AIP patients and 1 asymptomatic carrier) were identified as KTR. Baseline clinical characteristics of the KTRs are shown in the **Table 1** and the list of *HMBS* allelic variants is detailed in the **Table S1**.

AIP was diagnosed between 1976 and 2015 (median age at diagnosis, 35 years, range 21-53 years) and on average 19 years (range 0-31 years) before the diagnosis of ESRD except for one patient in whom the diagnosis of AIP was made 5 years after the initiation of dialysis. This patient reached ESRD in 2011 (the kidney disease was of undetermined cause at that time), and developed progressive peripheral neuropathy 2 years later, resulting in diagnostic uncertainty until AIP was proven with the identification of mutation in the *HMBS* gene in 2016.

These patients except the asymptomatic carrier experienced a median value of 4 attacks in their life before KTx (range 2-28), and 3 of them required heme-arginate maintenance therapy.

The etiology of kidney disease attributed at the time of ESRD diagnosis was: “unknown cause” in 3 cases, “AIP” in 3 cases, “chronic tubulointerstitial kidney disease” in 2 cases, and “nephroangiosclerosis” in 2 cases (**Table 1**). The asymptomatic carrier had a malformative uropathy (therefore a kidney disease unrelated to AIP). Familial cases of chronic kidney disease or ESRD have been identified in 3 KTRs. All patients were hypertensive. Six dialyzed patients (out of 8 under dialysis, 75%), developed visible light-exposed site bullae and skin fragility similar to as to those that occur during acquired porphyria cutanea tarda (PCT).

3.2. Kidney transplantation outcomes

These patients were transplanted between 2001 and 2017 and were followed in diverse transplant centers throughout France. Median age at KTx was 57 years (range 38-71 years), and all but 2 patients were female (**Table 2**). Three patients received a kidney transplant preemptively, and the rest of the group underwent dialysis therapy for a median period of

time of 2 years before transplantation (range 0-7), including 2 patients undergoing peritoneal dialysis. One patient received a living donor KTx, and one patient received a donation after cardiac death (DCD). All patients were followed for at least 5 years (median 9 years, range 0-15 years) after KTx except for the DCD patient who was transplanted in 2017, and a patient who died 2 months after KTx from cardiac arrest. No rejection episode was reported. No graft loss was noticed. At the last follow-up, median serum creatinine ~~47~~ 113 $\mu\text{mol/l}$ (range 73-196 $\mu\text{mol/l}$), and proteinuria was <0.5 g/l in all patients. Histology was unavailable for the great majority of kidney allografts.

In terms of infectious complications, 1 patient had recurrent urinary tract infections (treated with either cephalosporins or fluoroquinolones), 1 patient contracted hepatitis E virus (which was cured by ribavirin), another a CMV viremia, which resolved with valganciclovir. One patient had a nephrectomy for kidney cancer on a native kidney. One patient completed pregnancy without complication.

Most drugs usually are considered safe in patients with AIP (<http://www.drugs-porphyrin.org/>; <https://porphyriafoundation.org/>) with the exception of trimethoprim/sulfamethoxazole, which is porphyrinogenic, and therefore not recommended (**Table 3**). Atovaquone or aerosolized pentamidine were prescribed in all patients except 2, who received trimethoprim/sulfamethoxazole to treat a pneumonia caused by *Pneumocystis jiroveci* and for the primary prevention of pneumocystosis, without noticeable side effect.

3.3. AIP clinical activity after KTx

Skin lesions suggestive of PCT that had occurred in 6 AIP dialyzed patients (out of 8) disappeared after KTx (**Table 1**), with melanoderma as a sequel. Since the accumulation of porphyrins may cause skin lesion in ESRD patients with AIP, we explored the plasma porphyrin profile of these patients.

First, plasma total porphyrins could be measured before and after transplantation in the patient who received a kidney from controlled DCD. Primary non-function occurred after the KTx with the DCD kidney, and the patient received a second kidney transplant 18 months after the first KTx. Before the first KTx, the patient was on dialysis, and total plasma porphyrins levels remained steadily 20 times above the normal values (**Figure 2A**). After the first KTx, and despite the absence of renal function, total plasma porphyrins levels decreased and stabilized at a level less than 10 times the normal value. After the second KTx, renal function normalized, and plasma porphyrins reached near normal values (**Figure 2A**). Before KTx, the porphyrins profile of this patient was mostly made of uroporphyrin ($> 90\%$), whereas in PCT, both uroporphyrin and heptacarboxylporphyrin predominate due to a reduction of uroporphyrin decarboxylase activity (**Table 4** and **Figure 1**). In AIP patients with ESRD, uroporphyrin accumulation (mostly the isomer I, **Table S2**) derives from the

non-enzymatic polymerization and cyclisation of four molecules of PBG (**Figure 1**). Uroporphyrins promote lesions in regions of the skin exposed to the sun.

Consistent with the observation we made of the DCD KTR that plasma porphyrins concentrations decrease after KTx, the plasma porphyrin levels dramatically dropped after transplantation in 6 other KTRs in whom it was possible to perform the measurement (**Figure 2B**).

Acute attacks also almost disappeared after KTx. The occurrence of reported acute porphyria attacks before KTx ranged between 0.21/year and 5/year (median 0.29/year). After KTx, only 4 patients experienced 1 acute attack, and the rest of the cohort, none (**Table 2** and **Figure 3**). The impact of KTx on porphyrin precursors accumulation (which cause AIP symptoms) is exemplified in the DCD KTR by the dramatic reduction in plasma ALA and PBG concentrations after KTx: ALA 5.4 $\mu\text{mol/L}$ before, 1.6 $\mu\text{mol/L}$ after; PBG: 39.3 $\mu\text{mol/L}$ before, 3.4 $\mu\text{mol/L}$ after, PBG/ALA ratio: 7.2 before and 2.1 after. Since the accumulation of uroporphyrins in AIP patients with ESRD depends on the production and ALA and PBG, a drop in uroporphyrins concentrations after KTx is also consistent with the reduction of AIP activity (**Figure 2B**).

We also measured urinary ALA and PBG in a systematic way before and after transplantation in the patient who received a kidney from controlled DCD. However, the ALA and PBG urinary excretion profile is more complicated to interpret because the DCD KTx was oliguric for years before the second KTx, and measurement of urine ALA and PBG may be unreliable, and the urinary concentrations of ALA and PBG may not be a good indicator of disease activity. That being said, the excretion of urinary PBG and ALA remained above normal values before and after the successful KTx: mean urinary PBG 26.2 \pm 5.9 $\mu\text{mol/mmol}$ creatinine ($N < 1$ $\mu\text{mol/mmol}$ creatinine) before the second KTx, and 14.3 \pm 3.9 $\mu\text{mol/mmol}$ creatinine after the second KTx; mean urinary ALA 5.2 \pm 1.9 $\mu\text{mol/mmol}$ creatinine ($N < 3$ $\mu\text{mol/mmol}$ creatinine) before the second KTx, and 7.1 \pm 4.8 $\mu\text{mol/mmol}$ creatinine after the second KTx, indicating that precursors are still produced by the liver after KTx, and that transplantation of a heme-producing organ does not compensate the enzymatic deficit activity of the liver. However, when renal function returned to normal after the second KTx, the PBG/ALA ratio has significantly decreased (**Figure 4**): the mean PBG/ALA ratio (normal value < 0.3) was 5.1 \pm 2 before the second KTx and 1.6 \pm 0.2 after the second KTx. These results are consistent with previous findings [10], and our own experience (**Figure S1**), indicating that an increase of the urinary PBG/ALA ratio is associated with the decline of renal function in AIP patients.

4. Discussion

We provide evidence that KTx is the treatment of choice of AIP patients with ESRD. Even if the number of KTx patients in this cohort is small (AIP is a rare disease, and AIP patients rarely reach ESRD), we report the largest experience to date, and our data indicate that the post-transplantation history is simple without noticeable complication.

A major finding of our study is that KTx considerably decreases AIP activity. The most likely mechanistic hypothesis is that porphyrin precursors (ALA and PBG), which are responsible for the symptoms of acute porphyria, accumulate in parallel to the progression of renal failure. In turn, renal function improvement after KTx fosters precursors clearance and alleviates AIP symptoms. Supporting this notion, plasma measurements of ALA and PBG before dialysis sessions usually show a dramatic increase of precursors concentrations, especially PBG [10], and PBG and ALA are readily filtrated by dialysis membranes and concentrations decrease in plasma after dialysis session to about 70% of the value before dialysis; dialysis has even been proposed for the treatment of attacks when heme-arginate is not available [10, 17, 18]. Thus, the increased clearance of precursors after KTx is certainly responsible for the improvement of the symptoms of AIP. In addition, ALA, which is freely filtered by the kidneys, is reabsorbed in the proximal tubule by the human peptide transporter SLC15A2 [19]. If ALA is reabsorbed by a kidney allograft expressing functional HMBS, it will be metabolized into PBG, which, in turn, will be transformed into porphyrins. As a result, porphyrin precursors could accumulate in the organism in smaller quantities.

We also provide evidence that blistering lesions on sun-exposed skin that often occur in AIP dialyzed patients disappear after KTx. By definition, skin lesions and photosensitivity are not characteristic of AIP. Consistent with what was suggested for a long time [10], our results indicate that the very high concentration of porphyrins found in plasma of AIP patients undergoing dialysis is made of uroporphyrin I that derives from the non-enzymatic polymerization of the linear tetrapyrrole hydroxymethylbilane, and which spontaneously forms the cyclic tetrapyrrole uroporphyrin I (a compound unsuitable as an intermediate in the synthesis of protoporphyrin IX) (**Figure 1**) [20]. Uroporphyrin causes skin lesions in sun-exposed areas, resembling to those seen in PCT [10, 21, 22]. However, the plasma concentrations of porphyrins are not affected by dialysis therapy because these molecules are bound to plasma albumin. As a consequence, 75% of the dialyzed patients in our cohort suffered from photosensitivity and skin fragility resulting in vesicles and bullae of sun-exposed skin. Note that a similar disorder associated with bullous lesions in dialyzed patients called “pseudoporphyria” occurs in patients with normal porphyrins levels but clinical and histological features similar to those of PCT [23]. The disease appears to develop due to the association of photosensitizing medications and perhaps with an excessive ultraviolet exposure and the presence of uremic toxins [23, 24].

Our data also confirm previous observations made on the evolution of the PBG/ALA ratio during the progression of kidney disease: the PBG/ALA increases in parallel to the impairment of renal function, and a normalization the glomerular filtration rate is accompanied by a reduction of the ratio around values observed in AIP patients with normal renal function, that is approximately 2 [25]. The mechanisms supporting a selective accumulation of PBG over ALA during renal failure are not fully understood [10, 17, 26]. One can speculate that a reduction in porphyrin precursors clearance upon renal failure will primarily direct PBG since ALA will continue to be metabolized into PBG by ALA dehydratase, unlike PBG that will accumulate due to the HMBS enzymatic defect (**Figure 1**). The drug management after transplantation is unremarkable in AIP patients, and at the exception of trimethoprim-sulfamethoxazole, which is not recommended (but has been prescribed in 2 patients without side effect), all the drugs usually prescribed after KTx are authorized in AIP patients. The porphyrinogenicity of a drug is related to its capacity for induction of the rate-limiting enzyme in heme biosynthesis, ALAS1, and depends on chemical properties of the drug, structure and metabolism pointing to affinity to P450 cytochromes, hepatic load in therapeutic use, its capacity for P450 cytochrome induction or irreversible inhibition, and capacity to activate or modulate the transduction mechanisms of nuclear receptors affecting ALAS1 gene transcription [27]. In addition, a porphyrinogenic drug may not systematically trigger acute porphyric attacks, because the porphyric susceptibility of the patient depends on the gene mutation predisposing for acute porphyria, age and sex, previous and current disease activity, and recent or current exposure to other ALAS1-inducing agents [27]. It is thus proposed that in the absence of a safer alternative, an urgently needed drug should not be withheld on the grounds of its potential porphyrinogenicity.

Another important lesson of this study is that AIP should always be considered as one of the possible causes of chronic tubulointerstitial nephropathy, possibly associated with non-specific arteriolar lesions, of unknown cause, even if the patient is dialyzed. The identification of the disease is critical because it would lead to the diagnosis of AIP in the propositus family, and effective therapies targeting ALAS1 in the most severe forms of AIP are currently developed [28].

A limitation of this study is the lack of systematic pathological examination of kidney allograft biopsy specimen that would have provided information on the possible recurrence of PAKD in the kidney allograft. However, in the context of care, kidney biopsies were not indicated in almost all of these patients and the risk of a systematic screen for histological lesions would be superior to the expected benefits in terms of treatment. The risk of recurrence if PAKD is theoretically not excluded, but PAKD is a slowly progressive disease affecting AIP patients with a severe disease. Since AIP activity seems to turn off after KTx,

and some KTx have a normally functioning kidney allograft for more than 20 years, the risk of recurrence is likely to be low.

In conclusion, KTx is the treatment of choice of AIP patients with ESRD because the post-transplantation history is simple, and the drug management is easy. Critically, KTx reduces the disease activity in AIP patients and improve their quality of life.

Acknowledgements: none

Conflict of interest: This research was unfunded and the authors have no conflicts of interest to declare.

Authors' contributions:

Hélène Lazareth: involved in all aspects of study designs, data collection, data analysis, manuscript writing and final approval; Neila Talbi: involved in all aspects of study designs, data collection, data analysis, manuscript writing and final approval; Nassim Kamar: participated in clinical data collection & data analysis and manuscript writing/final approval; Charlene Levi: participated in clinical data collection & data analysis and manuscript writing/final approval; Bruno Moulin: participated clinical data collection, manuscript review/revising and final approval; Sophie Caillard: participated in clinical data collection, manuscript review/revising and final approval; Luc Frimat: participated in clinical data collection, manuscript review/revising and final approval; Jonathan Chemouny: participated in clinical data collection, manuscript review/revising and final approval; Valérie Chatelet: participated in clinical data collection, manuscript review/revising and final approval; Clément Vachey: participated in clinical data collection, manuscript review/revising and final approval; Renaud Snanoudj: participated in clinical data collection, manuscript review/revising and final approval; Thibaud Lefbvre: Valérie Chatelet: participated in clinical data collection, manuscript review/revising and final approval; Alexandre Karras: Valérie Chatelet: participated in clinical data collection, manuscript review/revising and final approval; Laurent Gouya: Valérie Chatelet: participated in clinical data collection, manuscript review/revising and final approval;; Caroline Schmitt: Valérie Chatelet: participated in clinical data collection, manuscript review/revising and final approval; Hervé Puy: participated in study design, clinical data interpretation, manuscript writing and final approval.

Nicolas Pallet: participated in study design, clinical data interpretation, manuscript writing and final approval.

Funding: none

Disclosures: all authors have approved the final article.

References

- [1] H. Puy, L. Gouya, J.C. Deybach, Porphyrias *Lancet* 375 (2010) 924-937.
- [2] D.M. Bissell, K.E. Anderson, H.L. Bonkovsky, Porphyria *N Engl J Med* 377 (2017) 862-872.
- [3] M. Siegesmund, A.M. van Tuyll van Serooskerken, P. Poblete-Gutierrez, J. Frank, The acute hepatic porphyrias: current status and future challenges *Best Pract Res Clin Gastroenterol* 24 (2010) 593-605.
- [4] B. Chen, C. Solis-Villa, J. Hakenberg, W. Qiao, R.R. Srinivasan, M. Yasuda, M. Balwani, D. Doheny, I. Peter, R. Chen, R.J. Desnick, Acute Intermittent Porphyria: Predicted Pathogenicity of HMBS Variants Indicates Extremely Low Penetrance of the Autosomal Dominant Disease *Hum Mutat* 37 (2016) 1215-1222.
- [5] Y. Nordmann, H. Puy, V. Da Silva, S. Simonin, A.M. Robreau, C. Bonaiti, L.N. Phung, J.C. Deybach, Acute intermittent porphyria: prevalence of mutations in the porphobilinogen deaminase gene in blood donors in France *J Intern Med* 242 (1997) 213-217.
- [6] G. Elder, P. Harper, M. Badminton, S. Sandberg, J.C. Deybach, The incidence of inherited porphyrias in Europe *J Inher Metab Dis* 36 (2013) 849-857.
- [7] J. Laafi, C. Homedan, C. Jacques, N. Gueguen, C. Schmitt, H. Puy, P. Reynier, M. Carmen Martinez, Y. Malthiery, Pro-oxidant effect of ALA is implicated in mitochondrial dysfunction of HepG2 cells *Biochimie* 106 (2014) 157-166.
- [8] H. Manceau, L. Gouya, H. Puy, Acute hepatic and erythropoietic porphyrias: from ALA synthases 1 and 2 to new molecular bases and treatments *Curr Opin Hematol* 24 (2017) 198-207.
- [9] N. Pallet, I. Mami, C. Schmitt, Z. Karim, A. Francois, M. Rabant, D. Nochy, L. Gouya, J.C. Deybach, Y. Xu-Dubois, E. Thervet, H. Puy, A. Karras, High prevalence of and potential mechanisms for chronic kidney disease in patients with acute intermittent porphyria *Kidney Int* 88 (2015) 386-395.
- [10] E. Sardh, D.E. Andersson, A. Henrichson, P. Harper, Porphyrin precursors and porphyrins in three patients with acute intermittent porphyria and end-stage renal disease under different therapy regimes *Cell Mol Biol (Noisy-le-grand)* 55 (2009) 66-71.
- [11] D.J. Nunez, P.F. Williams, A.L. Herrick, D.B. Evans, K.E. McColl, Renal transplantation for chronic renal failure in acute porphyria *Nephrol Dial Transplant* 2 (1987) 271-274.
- [12] G.W. Barone, B.J. Gurley, K.E. Anderson, B.L. Ketel, S.R. Abul-Ezz, The tolerability of newer immunosuppressive medications in a patient with acute intermittent porphyria *J Clin Pharmacol* 41 (2001) 113-115.
- [13] W. El-Haggan, T. Lobbedez, J.P. Ryckelynck, B. Hurault de Ligny, Sirolimus tolerability in a kidney transplant recipient with acute intermittent porphyria *Nephrol Dial Transplant* 17 (2002) 1147.
- [14] M.C. Tollanes, A.K. Aarsand, J.H. Villanger, E. Stole, J.C. Deybach, J. Marsden, J. To-Figueras, S. Sandberg, Establishing a network of specialist Porphyria centres - effects on diagnostic activities and services *Orphanet J Rare Dis* 7 (2012) 93.
- [15] H. Puy, J.C. Deybach, J. Lamoril, A.M. Robreau, V. Da Silva, L. Gouya, B. Grandchamp, Y. Nordmann, Molecular epidemiology and diagnosis of PBG deaminase gene defects in acute intermittent porphyria *Am J Hum Genet* 60 (1997) 1373-1383.
- [16] G.H. Elder, S.G. Smith, S.J. Smyth, Laboratory investigation of the porphyrias *Ann Clin Biochem* 27 (Pt 5) (1990) 395-412.
- [17] K. Miyagi, R. Cardinal, I. Bossenmaier, C.J. Watson, The serum porphobilinogen and hepatic porphobilinogen deaminase in normal and porphyric individuals *J Lab Clin Med* 78 (1971) 683-695.
- [18] M.R. Prabahar, R. Manorajan, D. Sathiyakumar, P. Soundararajan, M. Jayakumar, Hemodialysis: a therapeutic option for severe attacks of acute intermittent porphyria in developing countries *Hemodial Int* 12 (2008) 34-38.
- [19] D. Tchernitchko, Q. Tavernier, J. Lamoril, C. Schmitt, N. Talbi, S. Lyoumi, A.M. Robreau, Z. Karim, L. Gouya, E. Thervet, A. Karras, H. Puy, N. Pallet, A Variant of Peptide

Transporter 2 Predicts the Severity of Porphyrin-Associated Kidney Disease *J Am Soc Nephrol* 28 (2017) 1924-1932.

[20] I. Bogorad, Conference on Hemoglobin: 2–3 May 1957., Washington (DC): National Academies Press (US), 1958.

[21] S. Wahlin, P. Harper, E. Sardh, C. Andersson, D.E. Andersson, B.G. Ericzon, Combined liver and kidney transplantation in acute intermittent porphyria *Transpl Int* 23 (2010) e18-21.

[22] S.G. Smith, K.R. Rao, A.H. Jackson, The porphyrins of normal human urine, with a comparison of the excretion pattern in porphyria cutanea tarda *Int J Biochem* 12 (1980) 1081-1084.

[23] J.J. Green, S.M. Manders, Pseudoporphyria *J Am Acad Dermatol* 44 (2001) 100-108.

[24] F. Brivet, T. Drueke, J. Guillemette, J. Zingraff, J. Crosnier, Porphyrin cutanea tarda-like syndrome in hemodialyzed patients *Nephron* 20 (1978) 258-266.

[25] Y. Floderus, E. Sardh, C. Moller, C. Andersson, L. Rejkjaer, D.E. Andersson, P. Harper, Variations in porphobilinogen and 5-aminolevulinic acid concentrations in plasma and urine from asymptomatic carriers of the acute intermittent porphyria gene with increased porphyrin precursor excretion *Clin Chem* 52 (2006) 701-707.

[26] C. Unzu, A. Sampedro, E. Sardh, I. Mauleon, R. Enriquez de Salamanca, J. Prieto, E. Salido, P. Harper, A. Fontanellas, Renal failure affects the enzymatic activities of the three first steps in hepatic heme biosynthesis in the acute intermittent porphyria mouse *PLoS One* 7 (2012) e32978.

[27] S. Thunell, E. Pomp, A. Brun, Guide to drug porphyrogenicity prediction and drug prescription in the acute porphyrias *Br J Clin Pharmacol* 64 (2007) 668-679.

[28] L.J. Scott, Givosiran: First Approval *Drugs* 80 (2020) 335-339.

Corresponding author

Pr. Nicolas Pallet
Service de Biochimie, Hôpital Européen Georges Pompidou
20, rue Leblanc
75015 Paris, France
Phone: +33156092435; Fax: +33142862072
E-mail: nicolas.pallet@aphp.fr

Figure legends

Figure 1. Porphyrin metabolism and heme synthesis

In red, hydroxymethylbilane synthase, which is defective in Acute Intermittent Porphyria. In green, uroporphyrinogen III decarboxylase, which is defective in Porphyria Cutanea Tarda. Uroporphyrin I derives from the non-enzymatic polymerization of the linear tetrapyrrole hydroxymethylbilane, and spontaneously forms the cyclic tetrapyrrole uroporphyrin I (a compound unsuitable as an intermediate in the synthesis of protoporphyrin IX). As a negative feedback, heme inhibits ALA synthase 1 activity.

Figure 2. Plasma porphyrin profiles in KTR

A. Plasma concentration of total porphyrins in the DCD KTR before a first KTx, after KTx with a non-functioning kidney allograft, and after a second KTx with a normal renal function. Dash line represents normal value of total porphyrins in plasma (<20 nmol/l). **B.** Plasma concentration of total porphyrins in 6 other KTR before and after KTx.

Figure 3. Occurrence of AIP attacks before and after KTx. The number of acute porphyria attacks before and after KTx has been collected in the health records over an isometric period of time centered on the date of KTx, and which depends on the length of follow-up after KTx, and as such, vary according to patients. Note that Patient 11 is the asymptomatic carrier.

Figure 4. Porphyrin precursors profile in a KTR

Urinary PBG/ALA ratio in the DCD KTR before a first KTx, after KTx with a non-functioning kidney allograft, and after a second KTx with a normal renal function. Dash line represents normal value of PBG/ALA (=2) in urine in AIP patients with normal renal function.

Table 1. Baseline characteristics AIP and CKD

Continuous variables are expressed as median and range, and nominal variables are expressed as n and percentage. * asymptomatic carrier excluded; ** one patient received peritoneal dialysis and hemodialysis

Abbreviations: CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; AIP: Acute Intermittent Porphyria; KTx : Kidney Transplantation

	Overall (n=11)
AIP parameters	
Sex ratio (F/M)	9/2
Age at diagnosis-(years)	35 (21-53)
Asymptomatic carrier-(n,%)	1 (9)
Number of crisis before KTR *	4 (2-28)
Heme-arginate maintenance therapy (n,%)	3 (36)
Skin lesions-(n,%)	6 (54)
Hypertension-(n,%)	11 (100)
CKD parameters	
Primary CKD diagnosis-(n,%)	
Unknown cause	3 (36)
AIP	3 (36)
Chronic tubulointerstitial nephropathy	2 (18)
Hypertension	2 (18)
Malformative uropathy	1 (9)
Diabetes-(n,%)	0
Familial cases of kidney disease-(n,%)	3 (27)
Age at ESRD-(years)	55 (36-72)
Time between AIP diagnosis and ESRD-(years)	19 (0-31)
Dialysis modality-(n,%)**	
• Hemodialysis	7 (63)
• Peritoneal dialysis	2 (18)
• None (preemptive KTx)	3 (27)

Table 2. Characteristics of kidney transplant recipients with AIP

Continuous variables are expressed as median and range, and nominal variables are expressed as n and percentage. Normal value for proteinuria: 0.2 g/g. Normal range of value for serum creatinemia 49 to 90 $\mu\text{mol/L}$. Conversion factor for serum creatinin in $\mu\text{mol/l}$ to mg/dl, is /88.4.

	Overall (n=11)
Baseline parameters	
Age at KTx-(years)	57 (38-71)
Time from AIP to KTx-(years)	19 (0-31)
Preemptive KTx-(n,%)	3 (27)
Living donation-(n,%)	1 (9)
Donation after cardiac death-(n,%)	1 (9)
Delayed graft function-(n,%)	0
KTx outcomes	
Graft loss-(n,%)	0
Patient death-(n,%)	1 (9)
Acute rejection (cellular or antibody-mediated)- (n,%)	0
Hypertension-(n,%)	11 (100)
NODAT-(n,%)	1 (9)
Serum creatinine at last follow-up-($\mu\text{mol/l}$)	113 (73-196)
Proteinuria at last follow-up (g/g)	0.2 (0-0.4)
AIP outcomes after KTx	
Acute attacks reduction rate (before/after KTx)	21
Skin lesions resolution (%)	100

Table 3. List of the drugs prescribed to KTx in the cohort

<p>Immunosuppressive agents</p> <ul style="list-style-type: none"> • Thymoglobulines • Basiliximab • Prednisone • Azathioprine • Cyclosporine • Tacrolimus • Mycophenolate mofetil • Sirolimus 	<p>Antimicrobial agents</p> <ul style="list-style-type: none"> • Valganciclovir • Valaciclovir • Ribavirin • Aerosolized pentamidine • Atovaquone • Trimethoprim-sulfamethoxazole* • Ceftriaxone • Ofloxacin • Nitrofurantoin • Gentamicin 	<p>Analgesics/psychotropes</p> <ul style="list-style-type: none"> • Pregabalin • Gabapentin • Citalopram • Lormetazepam • Alverine • Midazolam • Fentanyl • Tramadol • Paracetamol
<p>Antihypertensive agents</p> <ul style="list-style-type: none"> • Atenolol • Bisoprolol • Spironolactone • Amlodipine • Nicardipine • Rilmenidine • Furosemide • Hydrochlorothiazide • Irbesartan • Ramipril • Prazosin • Nebivolol • Losartan 	<p>Cardiovascular system</p> <ul style="list-style-type: none"> • Aspirin • Heparin • Clopidogrel • Acenocoumarol • Rivaroxaban • Digoxin 	<p>Others</p> <ul style="list-style-type: none"> • Lansoprazole • Pantoprazole • Cinacalcet

* Porphyrinogenic drug

Table 4. Plasma porphyrins profiling in the DCD KTR patient in dialysis compared with a patient with Porphyria Cutanea Tarda

	Index KTR	Familial PCT
Total porphyrins (nmol/l)	531	210
Protoporphyrins (%)	1.1	0.8
Harderoporphyryns (%)	0	0
Coproporphyrins (%)	0.5	1.9
Pentacarboxylporphyrins (%)	0	5.7
Hexacarboxylporphyrins (%)	0	16.5
Heptacarboxylporphyrins (%)	6.5	28.3
Uroporphyrins (%)	92	39.9

Figure 1

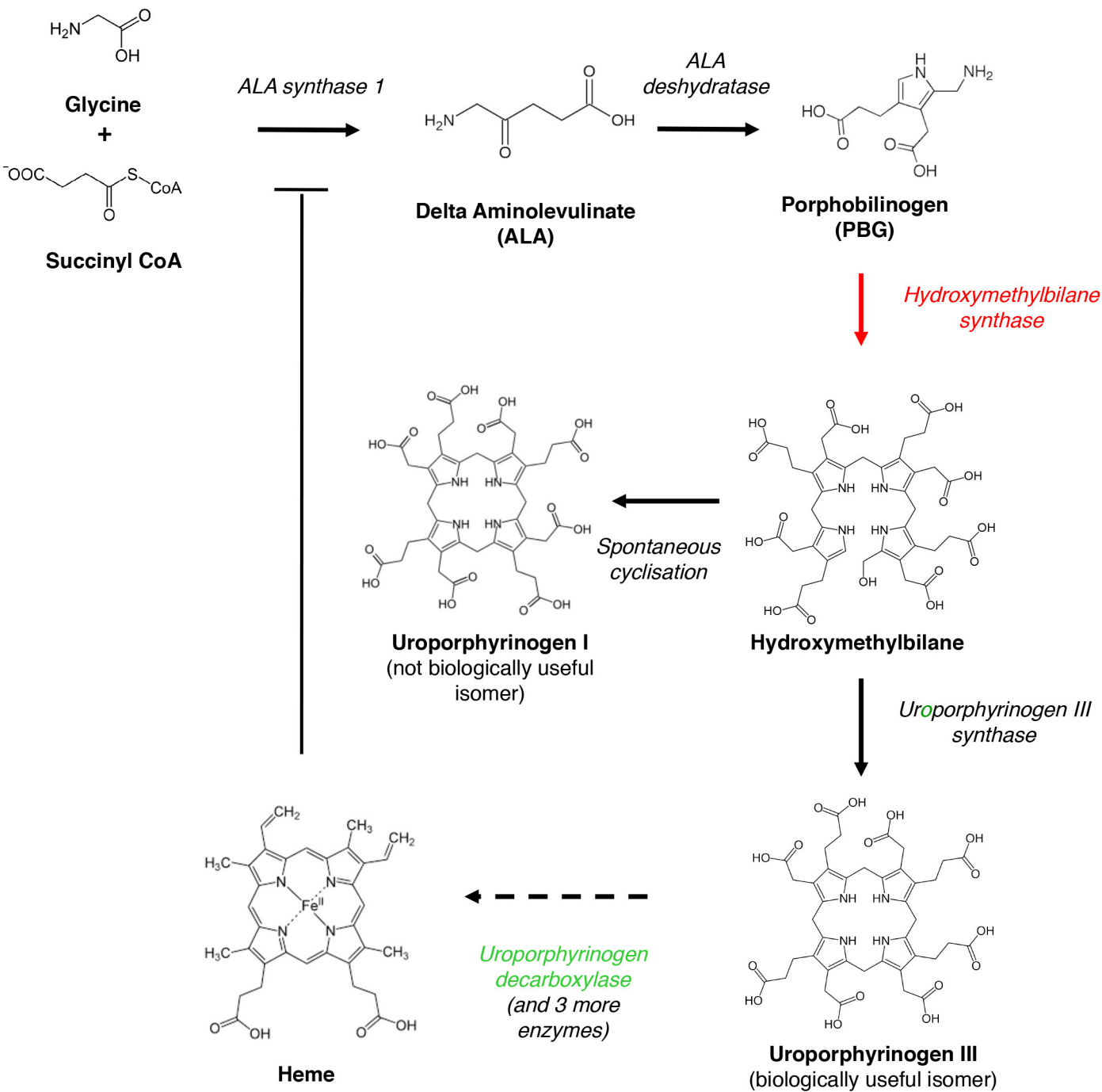
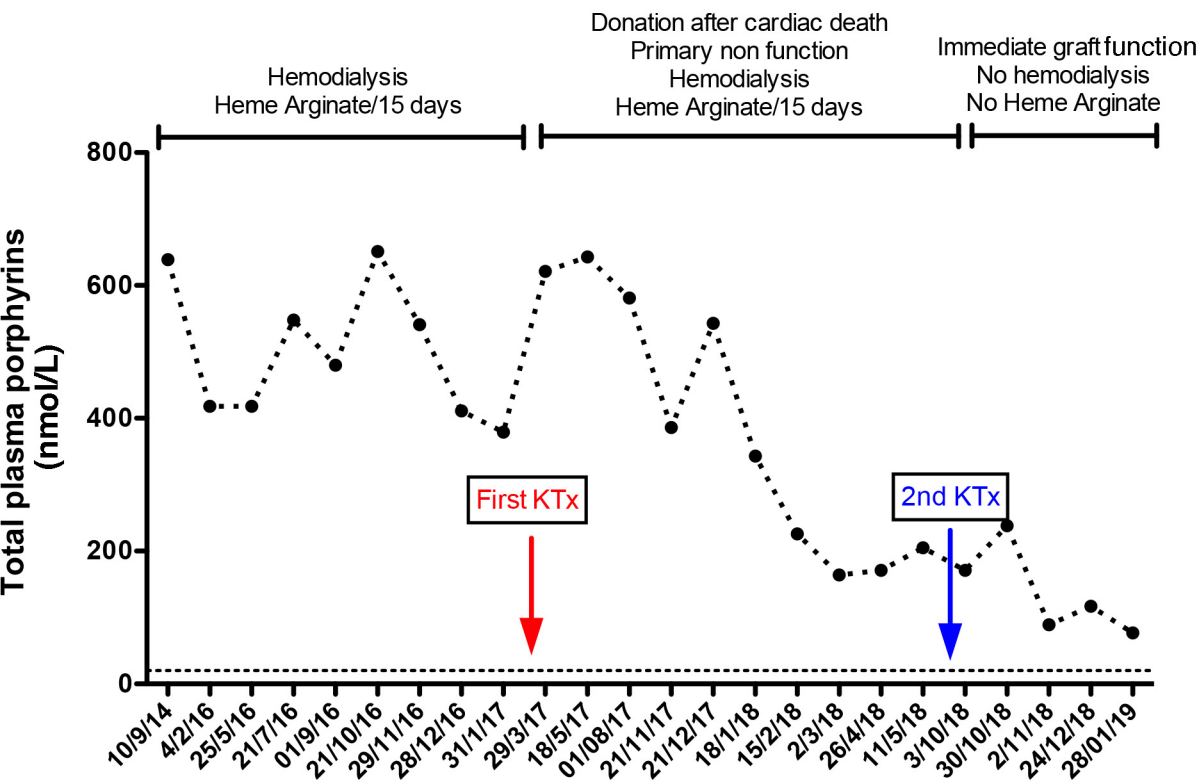


Figure 2

A



B

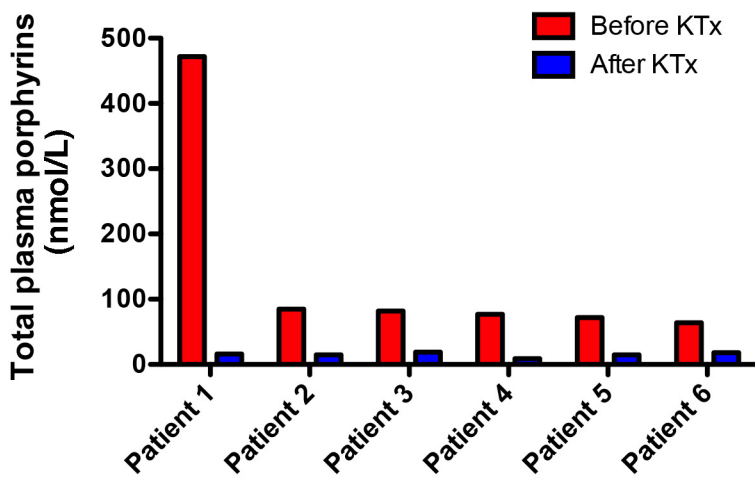


Figure 3

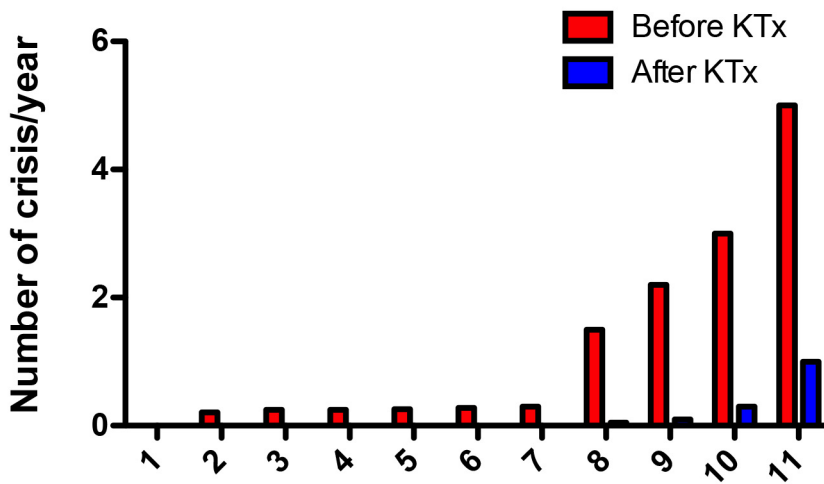


Figure 4

