Eliminating Hepatitis C Virus From a Prevalent Kidney Transplant Recipient Population: A Single-Center Study in Belgium in the Direct-Acting Antivirals Era

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ABSTRACT

Background. Direct-acting antivirals (DAAs) have revolutionized the treatment of hepatitis C virus (HCV) infection. Although previous studies have reported positive results with DAAs after kidney transplantation (KT), their impact on the prevalence of HCV viremia (HCVv) in prevalent kidney transplant recipients (KTRs) remains ill defined.

Methods. We retrospectively reviewed the HCV status of all patients followed at Cliniques Universitaires Saint-Luc, Brussels, Belgium, outpatient KT clinic between January 2014 and December 2018. We collected the clinical features of KTRs treated with DAAs during this period and calculated the annual prevalence of HCVv over this period.

Results. Out of 1451 KTRs, 22 (1.52%) had HCVv in 2014 to 2018. From 2014 to 2018, the annual prevalence of HCVv dropped from 1.97% to 0.43%, ($P < .001$). Fourteen KTRs were treated with DAAs a median of 197 months (range: 5-374) after KT, mostly (79%) in 2017 after reimbursement restrictions of DAAs for KTRs in Belgium were removed. DAA treatment was safe with a sustained virological response rate at 12 weeks after treatment (SVR12) of 93%. Two patients died 14 months (lymphoma, despite SVR12) and 7 months (hepatocarcinoma, no SVR12) after DAAs initiation, respectively. Among HCVv KTRs not treated with DAAs (n = 8), 2 lost their graft, 5 died, and 1 is initiating therapy. The current prevalence of HCVv in the cohort is 0.08%, with a single patient currently on treatment.

Conclusion. Treatment with DAAs led to a dramatic decrease of HCVv prevalence in this KTR cohort. DAA use was safe and effective. Elimination of HCV is possible at KT clinics.

HEPATITIS C virus (HCV) infection is a leading cause of chronic liver disease and liver-related deaths worldwide [1,2]. HCV infection affects 1.8% to 15% of kidney transplant recipients (KTRs) in high-income countries [3–6], a prevalence up to 10-fold higher than in the general population [7]. HCV-infected KTRs are at higher risk of chronic liver disease [8], new-onset diabetes mellitus [9], a post-transplant lymphoproliferative disorder (PTLD)

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[10,11], new-onset glomerular diseases [12,13], acute rejection [14], tuberculosis [15], graft failure, and death [9,16].

Until 2013, the only available treatment for chronic HCV infection was interferon alfa and ribavirin, which had poor efficacy [17], especially in patients with chronic kidney disease (CKD) and genotype 1 infection [18]. In addition, IFN-based therapy entailed a major risk of acute rejection, contraindicating its administration after transplantation [19]. The introduction of direct-acting antivirals (DAAs) for the treatment of HCV infection is one of the greatest advances of modern medicine. Treatment with DAAs achieves sustained virological response (SVR) rates $\geq$95% after 8 to 12 weeks of treatment [20]. It has also been demonstrated that DAAs can be used safely in HCV-infected patients with CKD with a similar SVR rate [21,22]. In prevalent KTRs, a randomized trial [23] and case series [24–30] have shown that DAAs can be used safely in KTRs with SVR 12 weeks after treatment (SVR12) rates of >90%.

In Belgium, DAAs have been available since 2015. However, from 2015 to 2017, DAAs were only refunded in KTRs with a liver fibrosis score $\geq$F2. DAAs have been fully refunded for all HCV viremic (HCVv) KTRs (independently of liver fibrosis score) since January 2017, and all reimbursement restrictions were removed in January 2019.

The aims of this single-center retrospective study were to assess: (1) the annual prevalence of HCVv in KTRs in our cohort over the last 5 years; and (2) whether the introduction of DAAs has impacted the prevalence of HCVv in KTRs.

MATERIAL AND METHODS

Patient Selection

Between January 2014 and December 2018, 1451 KTRs were followed at the outpatient KT clinic in Cliniques Universitaires Saint-Luc, Brussels, Belgium. HCV serology is performed in all KTRs at the time of wait-listing, on day of transplantation, and then at least every 2 years. All KTRs with a confirmed positive HCV serology (two positive consecutive tests) have a polymerase chain reaction (PCR) test to detect HCV ribonucleic acid (RNA). Figure 1 shows the flow chart of the HCVv in KTRs. From the 54 KTRs with a positive HCV serology, 22 KTRs had HCVv positive PCR during transplantation (transplanted from December 1985 to March 2017). Patients were followed until death, allograft failure, or end of the study.

Microbiological Investigations

HCV antibody detection was carried out by a qualitative electrochemiluminescence immunoassay with the Elecsys Anti-HCV II assay on the cobas 8000 platform (Roche Diagnostics GmbH, Penzberg, Germany). HCV viral load was measured by reverse transcriptase real-time PCR (RT-qPCR) with the Abbott RealTime HCV kit on the m2000 system (Abbott, Illinois, United States).

Prevalence

We calculated the annual prevalence of HCVv in KTRs at the end of each year, as the ratio between the number of HCVv KTRs and the total number of patients coming at the outpatient KT clinic at least once during the year of interest. We assessed the total number of patients followed at the outpatient KT clinic based on the Information Technology appointment system: 965 KTRs were seen at least once in 2014, 996 in 2015, 1015 in 2016, 1006 in 2017, and 1158 in 2018. Importantly, our local protocol requires that all KTRs visit our clinic at least once a year. If a KTR died or lost his or her graft during a year of interest, the patient was included in the analysis until that year, but not subsequently. If a KTR was HCV viremic at least 1 day during a year of interest (even if the KTR was successfully treated during this year), the individual was considered HCVv positive in the calculation of the annual prevalence of that year, but not subsequently. As PCR was not performed repeatedly until DAAs became available, patients were considered as HCVv from the first positive HCV PCR to post-treatment laboratory-proven PCR negativation unless a laboratory-proven spontaneous clearance was assessed (very rare in immunosuppressed patients) [31].

Statistics

Results are presented as the median and range for continuous variables. Frequencies of categorical variables are presented as numbers and percentages. For statistical comparison of the trend of HCVv prevalence over years, we used the Fisher exact test. Analyses were performed with R software (version 3.1.3; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics of HCV Viremic KTRs

Table 1 summarizes the baseline characteristics of the HCVv KTR cohort at transplantation (n = 22). The median age was 48 (range: 19-70) with 50% female patients. Causes of end-stage renal disease were glomerulonephritis

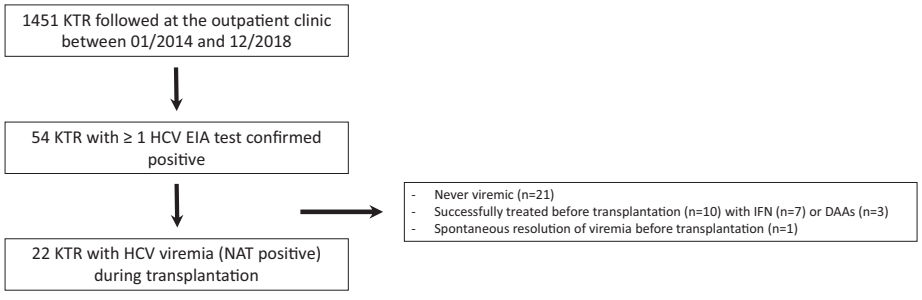


Fig 1. Flowchart selection of hepatitis C virus viremic kidney transplant recipients. DAAs, direct-acting antivirals; EIA, enzyme immunoassay; HCV, hepatitis C virus; IFN, interferon; KTR, kidney transplant recipient; NAT, nucleic acid testing.

Table 1. Baseline Characteristics of the Hepatitis C Virus Viremic Cohort at Transplantation

Viremic Population (n = 22)	
Age at transplantation, y, median (range)	48 (19-70)
Male recipients, n (%)	11 (50%)
Cause of ESRD, n (%)	
Glomerulonephritis	7 (32%)
HCV-mediated GN	1 (5%)
Diabetes mellitus	2 (9%)
ADPKD	3 (14%)
Chronic interstitial nephritis	1 (5%)
Urologic malformation	2 (9%)
Other/undetermined	7 (32%)
First transplantation, n (%)	20 (91%)
Living donor, n (%)	4 (18%)
Isolated kidney transplantation, n (%)	18 (82%)
Combined kidney-pancreas transplantation, n (%)	1 (5%)
Combined liver-kidney transplantation, n (%)*	3 (14%)
HCV genotypes	
Unknown, n (%)	1 (5%)
Genotype 1, n (%)	10 (45%)
Genotype 2, n (%)	4 (18%)
Genotype 4, n (%)	6 (27%)
Genotype 3-4 co-infection, n (%)	1 (5%)

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease; GN, glomerulonephritis; HCV, hepatitis C virus.
*Causes of liver transplantation: polycystosis (n = 1), HCV cirrhosis complicated by hepatocarcinoma (n = 2). One patient had a liver transplantation 5 years after the kidney transplantation.

(32%), diabetes mellitus (9%), autosomal dominant polycystic kidney disease (14%), chronic interstitial nephritis (5%), urologic malformation (9%), and others/undetermined (32%). For a large majority (91%), it was a first transplantation, with 18% of KTR transplantation from a living donor. Only 3 patients underwent combined liver-KT (1 patient had a liver transplantation 5 years after the KT). Of these patients, 2 received a liver for HCV-mediated complication (HCV cirrhosis complicated by hepatocarcinoma [HCC]). HCV genotypes were 1 (45%), 2 (18%), 4 (27%), 3-4 co-infection (5%), and unknown (5%), respectively.

Evolution and Management of HCV Viremic KTRs

Twenty-two KTRs were HCVv after transplantation. Fourteen KTRs were treated with DAAs while having a functioning graft and are described in the following paragraph. Among those not treated with DAAs (n = 8) (Fig 2), 2 patients (#15 and #22) had lost their grafts in 2014 and 2015, respectively, before full reimbursement availability of DAAs in Belgium (in 2017). Both were successfully treated with DAAs while on chronic dialysis after graft loss. Five KTRs died before DAA treatment initiation (patients #16, #17, #19, and #20 while listed for DAA treatment, and patient #21, who died in 2014 before treatment availability) from septic shock, stroke, heart failure, postoperative hemorrhagic shock, and undetermined cause, respectively. Patient #18 has just started DAA treatment.

Evolution and Management of HCV Viremic KTRs Treated With DAAs

Fourteen (64%) KTRs were treated with DAAs while having a functioning graft, a median of 197 months (range: 5-374) after transplantation (Table 2). HCV genotypes were type 1 (n = 6), type 2 (n = 4), and type 4 (n = 4). Five combinations of antivirals had been used: elbasvir/grazoprevir (n = 5), sofosbuvir/velpatasvir (n = 4), sofosbuvir/daclatasvir (n = 2), sofosbuvir/ledipasvir (n = 2), and ombitasvir/paritaprevir/dasabuvir (n = 1). Treatment initiation rates dramatically increased in the year 2017 (Table 2 and Fig 2). Out of the 14 treated KTRs, 8 (57%) required calcineurin inhibitor (CNI) dose adjustment during DAA treatment (5 required CNI dose reduction and 3 CNI dose increase).

After a median follow-up time of 18 months (range: 6-35) after DAAs initiation, no patient experienced biopsy-proven acute rejection or de novo donor-specific antibody occurrence after DAA treatment (Table 2 and Fig 2). All patients had at least 1 anti–human leukocyte antibody assessment by single-antigen technique after DAA treatment. Median estimated glomerular filtration rate (calculated by CKD-Epidemiology Collaboration formula) remained stable after DAA treatment (44 [range: 30-97] mL/min/1.73 m^2 before DAAs initiation vs 45 [range: 23-101] mL/min/1.73 m^2 at the end of treatment vs 42 [range: 5-101] mL/min/1.73 m^2 at last follow-up), and no KTRs treated with DAAs experienced graft loss. However, patient #3 experienced severe allograft dysfunction at the end of follow-up with imminent need of dialysis. He was a male patient born in 1943 who received a kidney transplant in 1994 for HCV (genotype 2)-induced cryoglobulinemic glomerulonephritis. This patient developed heavy proteinuria in 2012, and allograft biopsy performed in 2014 showed focal and segmental glomerulosclerosis with no sign of initial disease recurrence or acute rejection. In September 2017, DAAs (sofosbuvir/velpatasvir) were initiated and well tolerated. However, at the time of DAAs initiation, the patient showed impaired estimated glomerular filtration rate (33 mL/min/1.73 m^2) and heavy proteinuria (urine protein/creatinine ratio at 2.54 g/g). After DAA treatment, allograft function and proteinuria worsened (Table 2). No allograft biopsy was performed. At the time of data cut-off, 16 months after DAAs initiation, dialysis was imminent, and the patient was listed for a second KT.

Two patients died after DAA treatment (Fig 2). Patient #6 was a male patient born in 1949 and received a kidney transplant in 1985 for diabetic nephropathy. He was known since 1994 for HCV genotype 1 viremia without liver enzyme abnormalities. In February 2017, DAAs (ledipasvir/sofosbuvir) were initiated. DAAs were well tolerated without any side effects, and the patient achieved SVR12. However, in February 2018, the patient reported malaise, decreased appetite, abdominal pain, and weight loss. Retroperitoneal B-cell PTLD was diagnosed. Because of impaired general status and the patient's preference for no aggressive treatment, chemotherapy was not initiated, and the patient died 4 months later.

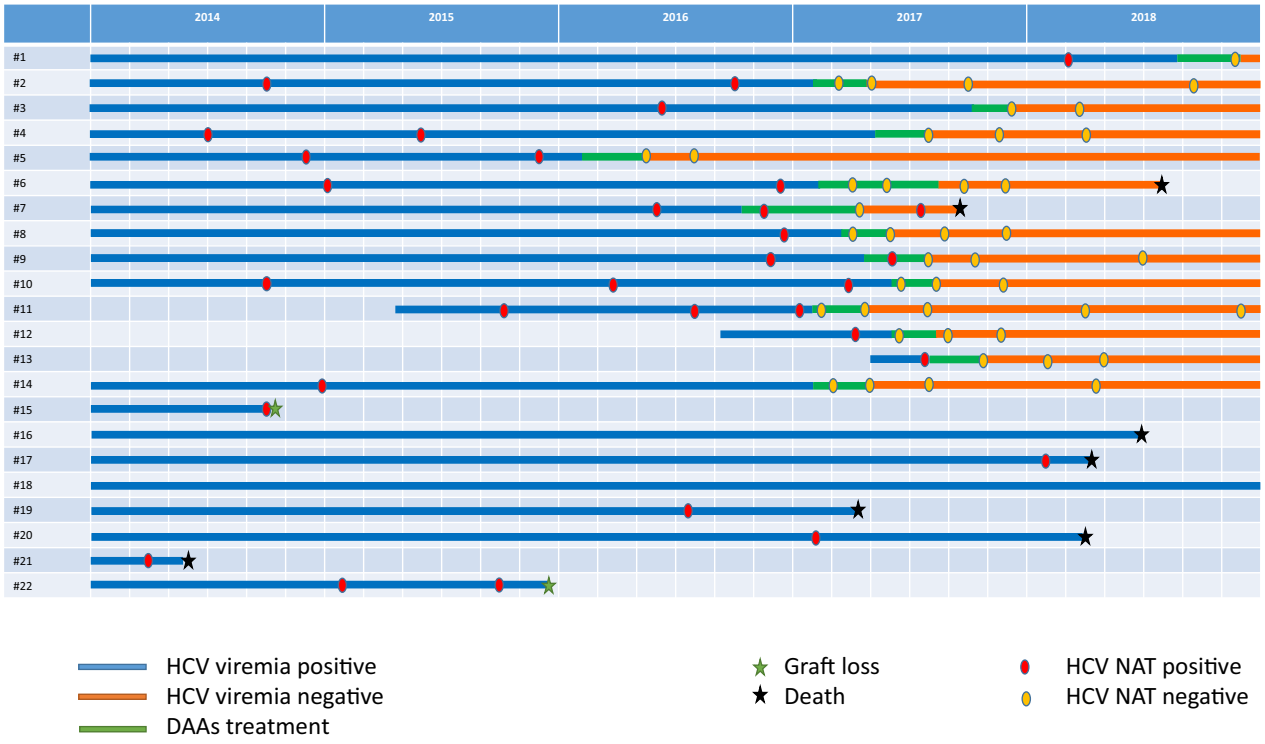


Fig 2. Clinical evolution of the 22 hepatitis C virus viremic kidney transplant recipients in the 2014 to 2018 period. DAAs, direct-acting antivirals; HCV, hepatitis C virus; NAT, nucleic acid testing.

Patient #7 was a female patient born in 1953 who received a kidney transplant in 2000 for chronic pyelonephritis and subsequently received a liver transplant in 2005 for a genotype 1 HCV-induced HCC. Liver biopsy in June 2015 showed recurrence of HCV hepatitis with a F1 METAVIR score. In January 2016, abdominal magnetic resonance imaging (MRI) was normal and alpha-fetoprotein (AFP) level was at 5.8 ng/mL (normal <9 ng/mL). In October 2016, DAAs (ledipasvir/sofosbuvir) were initiated and well tolerated. She achieved viral response at the end of treatment in April 2017. However, SVR12 assessment in July 2017 showed recurrence of HCVv. Concomitantly, the patient reported general malaise and abdominal pain. Alpha-fetoprotein level was increased at 41.5 μg/L, and abdominal MRI revealed multiple hepatic masses compatible with a diffuse HCC, with a high suspicion of pulmonary metastases at chest x-ray. Biopsy of a hepatic lesion confirmed HCC diagnosis. The patient died 1 month later.

With the exception of patient #7, all KTRs treated with DAAs achieved SVR12 (rate 93%) (Table 2).

Annual Prevalence of HCVv in KTRs

The annual prevalence of HCVv in KTRs was 1.97% in 2014, 1.81% in 2015, 1.77% in 2016, 1.69% in 2017, and 0.43% in 2018 ($P < .001$) (Fig 3). Interestingly, we observed a dramatic drop of HCVv in 2018 in line with the increased rate of DAAs initiation in 2017 (Table 2 and Fig 2). Currently, the prevalence of HCVv in our cohort of KTRs with functioning graft is 0.08% and will be 0% if the last patient (#18), who is starting DAA treatment, reaches SVR12.

DISCUSSION

The modification of the Belgian reimbursement of DAAs has drastically modified the epidemiology of HCVv among KTRs. Indeed, all HCV-infected KTRs with a functioning allograft have been treated (1patient still under treatment), mostly after January 2017. As a consequence, we hope, HCVv will soon be totally eliminated from our KTR cohort.

DAAs are such a revolution in the management of HCV infection that the World Health Organization has set the goal to eliminate HCV in all countries by 2030 [32]. The optimal strategy to reach this ambitious goal remains controversial and challenging owing to both the difficulty organizing effective elimination globally and the high cost of DAAs, despite recent declines in prices [2]. An economic analysis revealed that the current prices of DAAs were globally unaffordable and threaten the sustainability of many national health systems to eliminate HCV across the 30 countries investigated [33].

The microelimination approach, consisting of first eliminating HCV in well-defined high-risk groups, is another option. It is less daunting, less complex, and less costly than

Table 2. Patients Treated With Direct-Acting Antivirals

Patient	Genotype	Prior IFN	Year of KT	Year of DAA initiation	Months From KT to DAA Start	Liver Fibrosis Score Assessment	DAA Regimen	IS at DAA Initiation	eGFR Before DAAs Start*	P/Cr Ratio Before DAAs start†	eGFR at EOT*	eGFR at Last F/U*	P/Cr Ratio at Last F/U†	SVR12	CNI Dose Adaptation During DAAs Treatment	Follow-up From DAAs Initiation
1	1	No	1988	2018	362	F0	SOF/VEL	Csa/Aza/st	54	0.09	56	70	0.24	Yes	Decrease	6 months
2	2	No	1996	2017	252	F4	SOF/VEL	Csa/Aza/st	97	0.15	101	101	0.08	Yes	Decrease	23 months
3	2	No	1994	2017	276	F0	SOF/VEL	Csa/Aza/st	33	2.54	23	5	8.9	Yes	No	16 months, listed for a second TP
4	2	No	1988	2017	347	F0-F1	SOF/VEL	Csa/MPA/st	71	0.08	79	78	0.14	Yes	No	13 months
5	1	No	1990	2016	189	F4	OMB/PAR/DASA	Csa/st	43	0.23	42	39	0.41	Yes	Decrease	35 months
6	1	No	1985	2017	374	F2	SOF/LED	Csa/st	39	0.24	42	42	1.2	Yes	Decrease	16 months, death (PTLD)
7	1	No	2000	2016	204	F1	SOF/LED	Tac	49	0.07	55	57	NA	No	Increase	11 months, death (HCC)
8	1	No	2005	2017	166	F0-F1	ELB/GRA	Tac/Aza	30	0.23	28	30	0.13	Yes	No	21 months
9	4	Yes	1998	2017	226	F2	ELB/GRA	Tac/MPA	38	0.14	35	38	0.67	Yes	No	20 months
10	4	Yes	2013	2017	36	F2	ELB/GRA	Tac/MPA/st	44	0.54	52	50	0.65	Yes	No	20 months
11	4	No	2015	2017	21	F0-F1	SOF/DAC	Tac/MPA/st	45	0.22	47	37	0.10	Yes	Increase	24 months
12	1	No	2016	2017	7	F0-F1	ELB/GRA	Tac/MPA/st	34	0.41	36	38	0.13	Yes	Decrease	19 months
13	4	No	2017	2017	5	F0-F1	ELB/GRA	Tac/MPA/st	46	0.23	54	62	0.05	Yes	Increase	16 months
14	2	No	2004	2017	148	F0	SOF/DAC	Tac/MPA/st	40	0.07	41	42	0.10	Yes	No	16 months

Abbreviations: Aza, azathioprine; Csa, cyclosporine; CNI, calcineurin inhibitors; DAAs, direct-acting antivirals; eGFR, estimated glomerular filtration rate; ELB/GRA, elbasvir/grazoprevir; EOT, end of treatment; F/U, follow-up; HCC, hepatocarcinoma; IFN, interferon alfa; IS, immunosuppressive regimen; KT, kidney transplantation; MPA, mycophenolic acid; OMB/PAR/DASA, ombitasvir/paritaprevir/dasabuvir; P/Cr, protein/creatinine; PTLD, post-transplant lymphoproliferative disorder; st, steroids; SOF/DAC, sofosbuvir/daclatasvir; SOF/LED, sofosbuvir/ledipasvir; SOF/VEL, sofosbuvir/velpatasvir; SVR12, sustained virological response 12 weeks after treatment; Tac, tacrolimus.

*mL/min/1.73 m^2 (CKD-Epidemiology Collaboration formula).

†g/g of creatinine.

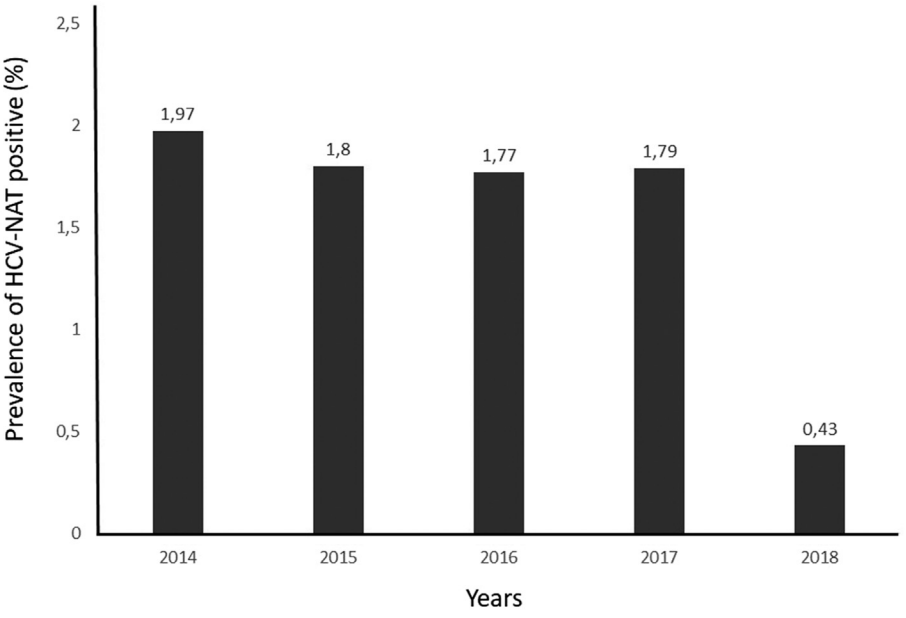


Fig 3. Evolution of the annual prevalence of hepatitis C virus viremic kidney transplant recipients in the 2014 to 2018 period. HCV, hepatitis C virus; NAT, nucleic acid testing.

full-scale, country-level initiatives to eliminate HCV [34]. In this regard, the transplant and the nephrology communities have a key role to play regarding the higher reported prevalence of HCV infection among KTRs and chronic dialyzed patients compared to the general population [3–6,22]. In addition, the recently published retrospective review of the French database showed that in HCV infected patients, KTRs with detectable HCVv had poorer 10-year graft and patient survivals compared to matched unaffected controls, while outcomes of patients with undetectable viremia were similar to those of patients not infected [35]. It strongly suggests that DAAs should be proposed to all KTR and KT candidates.

Our study shows that HCV elimination is possible in KTRs. All kidney transplant centers should screen and treat all KTRs with HCVv. Moreover, the 2018 update of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the management of HCV infection in patients with CKD recommends treating CKD patients (including chronic dialyzed patients) with DAAs before KT [36]. This would translate, in the near future, to the cure of HCV in kidney transplant candidates before undergoing transplantation.

DAA treatment was safe and effective in our KTRs with an SVR12 rate at 93%. None of the patients experienced acute rejection or de novo donor-specific antibody development after DAA treatment. Allograft function also remained stable. However, as in previous studies, our follow-up was quite short, and we lack pre- and post-treatment graft biopsies to explore in-depth if DAAs are not associated with long-term nephrotoxicity, as recently suggested by others [37]. In the present study, no graft loss was observed, but 1 patient (#3) had severe allograft dysfunction with imminent need for dialysis 16 months after DAAs initiation. Pre-existing allograft dysfunction and heavy proteinuria most likely accounted for the end-stage graft function. However, we cannot totally exclude a potential negative effect of DAA treatment, especially without histologic information.

In our treated patients, we found that roughly 50% of patients require dose adjustment during DAA treatment. This is in agreement with other reports [25,29,38] The reason is not clearly explained but could reflect enhanced CNI metabolism associated with improvement of liver injury [25] or could be an indirect marker of the clearance of chronic HCV infection that produce pro-inflammatory cytokines that may inhibit cytochrome P450 enzymes [39]. Hence, physicians should closely monitor CNI and adjust their dose during and after DAA treatment.

If DAA treatment seems safe and effective after KT, long-term follow-up is still lacking to assess if HCV elimination after KT can reverse the HCV-related complications. Even if our cohort of KTRs treated with DAAs is too small to make solid definitive conclusions, it is important to note that 2 KTRs died after DAAs treatment of PTLD and HCC, 2 potential HCV-related complications [10,11,40]. HCC is a dreadful complication and survival after HCC diagnosis in KTR has been reported to be significantly worse as compared to nontransplanted patients [41]. The risk of de novo HCC or HCC recurrence after DAAs is not well defined, even in the nontransplant setting. Two studies published in 2016 revealed that the incidences of HCC recurrence post-DAA treatment or de novo HCC occurrence were higher than expected [42,43] Roche et al [44] recently published a review article in the nontransplant setting including mostly retrospective studies [44]. The incidence of de novo HCC after DAAs treatment ranges from 0.9% to 9.1% and those of HCC recurrence from 12%

to 29.8%. As a consequence, surveillance for HCC is recommended with biannual liver imaging for patients with advanced fibrosis (F3 or F4) who achieve SVR [45]. The same recommendations apply in the KT setting [36].

One limitation of our study is that it is retrospective, making it subject to reporting bias. In particular, if an HCVv KTR did not present to the outpatient KT clinic from 2014 to 2018, the case was missed in the prevalence analysis. However, this situation seems quite unlikely and marginal. Also, the follow-up time post-DAA treatment was quite short (6-35 months), and allograft biopsies were not available, preventing the assessment of allograft toxicity induced by DAAs.

In conclusion, treatment with DAAs was safe and effective in our KTR cohort with a SVR12 rate at 93%. It led to a dramatic decrease of HCVv prevalence. Elimination of HCV is finally at reach in this population.

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