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People living with HIV hospitalised for kidney disease: a nationwide survey

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Abstract (299 words)

Objectives: To describe hospitalisations for kidney disease (KD) among persons living with HIV (PLHIV) in France and to identify the factors associated with such hospitalisations since data on the epidemiology of KD leading to hospitalisation are globally scarce.

Design: Observational nationwide study using the French PMSI (Programme de Médicalisation des Systèmes d'Information) database.

Setting: France 2008-2013

Participants: Around 10,862 PLHIV out of a mean of 5,210,856 patients hospitalised each year. All hospital admissions with a main diagnosis code indicating KD (ICD-10 codes N00 to N39) were collected.

Main outcome measures: The prevalence and incidence of KD leading to hospital admission in PLHIV and the associated risk factors..

Results: The prevalence of patients hospitalised for KD was 1.5 higher in PLHIV than in the general population, and increased significantly from 3.0% in 2008 to 3.7% in 2013 ($P < 0.01$). The main cause of hospitalisation for KD was acute renal failure (ARF, 25.4%). Glomerular diseases remained stable (6.4%) throughout the study period, focal segmental glomerulosclerosis being the main diagnosis (37.6%). Only 41.3% of patients hospitalised for glomerular disease were biopsied. The other common motives for admission were nephrolithiasis (22.1%) and pyelonephritis (22.6%).

The 5-year cumulative incidence of KD requiring hospitalisation was 5.9% in HIV patients newly diagnosed for HIV in 2009. Factors associated with a higher risk of incident KD requiring hospitalisation were age (OR=1.02, 1.00 to 1.04), cardiovascular disease (OR=3.39, 1.22 to 9.42), and, for female patients, AIDS (OR=3.67, 1.26 to 10.70). Two thirds of hospitalisations for incident ARF occurred in the first two years of follow-up.

Conclusions: Hospital admission for KD is more frequent in PLHIV than in the general population and increases over time. ARF remains the leading cause. Glomerular diseases are infrequently documented by renal biopsies. Older patients and those with cardiovascular disease are particularly concerned.

Strengths and limitations of this study

- This study is the first to focus on hospital admissions for kidney disease (KD) in a large population people living with HIV (PLHIV).
- This study is a nationwide 5-year study on a mean of 10,862 PLHIV hospitalized, i.e. about 10% of the estimated cohort of 110,900 PLHIV medically followed-up in France, out of a mean of 5,210,856 patients hospitalised each year.
- It shows that the prevalence of patients hospitalised for KD is 1.5 higher in PLHIV than in the general population, and increases over time, and a 5-year cumulative incidence of 5.9%.
- The exhaustive nature of our data ensures that the results are representative of all hospitalisations for KD in France.
- The main limitation is the use of administrative codes, even though they are based on the clinical judgment of physicians and laboratory values. It was also not possible to provide accurate characteristics of the HIV infection

Keywords: HIV; kidney disease; acute renal failure; glomerular disease; hospitalisation

Introduction

In 2015, 36.9 million people around the world and about 130,000 in France were living with HIV. The introduction of highly active antiretroviral therapy (HAART) has dramatically decreased mortality and significantly improved the quality of life of people living with HIV (PLHIV). However, an increase in the incidence of co-morbidities, including kidney disease (KD), has been observed [1 2]. Several studies have shown that acute renal failure (ARF) was three to four times more frequent in PLHIV than in the general population [3 4] and that its incidence did not decrease as HAART became more common [5]. ARF, in the general population and PLHIV, has also been associated with longer hospital stays and higher costs, and with a risk of progression to chronic KD (CKD) [6-8].

The incidence of CKD is reportedly higher in PLHIV than in people not infected with HIV [9]. Its prevalence has been estimated at between 1% in the D.A.D study [10] and 4.9% in a French cohort of 2,588 patients [11]. The proportion of HIV-associated nephropathy (HIVAN) has significantly fallen [12], while that of other KDs, such as classical focal segmental glomerulosclerosis (FSGS) or HIV-associated immune complex KD (HIVICK), has increased [13]. The increase in the incidence of CKD could also be related to the nephrotoxicity of some antiretroviral drugs or to the increased frequency of co-morbidities, such as diabetes, hypertension, cardiovascular disease, or hepatitis C or B coinfection [6 10 14].

However, to our knowledge, no studies have dealt with the epidemiology of KD leading to hospitalisation in PLHIV in the recent HAART era. We thus conducted a national observational study to describe hospital admissions for KD in PLHIV in France and to identify factors associated with such admissions.

Patients and Methods

This study was an observational retrospective multicentre study based on nationwide PMSI (Programme de Médicalisation des Systèmes d'Information) data from 2008 to 2013. The French PMSI database is similar to the Medicare database and includes all admissions in all hospitals from 1997 onwards. Since 2007, it has been possible to link all discharge abstracts for a single patient. Diagnoses identified during hospital stays are coded according to the tenth edition of the International Classification of Diseases (ICD-10). This database

provides a vast amount of epidemiological information regarding hospitalised patients in France [15-18], is truly representative, and can be used to detect rare events.

In the first part of the study, all patients older than 18 years hospitalised with a main or associated diagnosis of HIV infection (ICD-10 code B20-24, Z21) were eligible. All patients with at least one hospitalisation lasting more than 24 hours were included. Those hospitalised for less than 24 hours were excluded since repeated short hospitalisations were most often regular follow-up consultations or ambulatory care. Age, sex, comorbidities and patient outcomes in the year following hospitalisation were collected. Each patient was classified as having past or present AIDS-defining illness (Centers for Disease Control (CDC) Stage C, codes B20-22, B241) or being HIV infected without progression to AIDS (CDC stages A and B, codes B23, B240, B249, and Z21). Hospital admissions with a main diagnosis code corresponding to KD (ICD-10 codes N00 to N39) in the year following the first hospitalisation with a diagnosis of HIV infection were collected. The KDs were defined and classified as follows: acute renal failure (codes N17 and 19), chronic KD either at first diagnosis or with associated complications, acute renal failure (code N18), nephrolithiasis (codes N13, 20, 21, 22 and 23), pyelonephritis (codes N10, 11, 12 and 15), renal parenchymal diseases (including glomerular and tubular diseases) (codes N01-06, N08, N14, N16 and N25), and other KD (codes N26, 27, 28, 29 and N39). For glomerular diseases, both the syndrome (e.g. nephrotic syndrome) and the related disease (e.g. membranous nephropathy) were available. The identified syndromes were haematuria, proteinuria, nephrotic syndrome, and acute or chronic nephritic syndrome. Comorbidities were also collected: hypertension (codes I10-I15), diabetes mellitus (codes E10-E14), dyslipidaemia (code E78), heart failure (code I50), coinfection with hepatitis B and / or hepatitis C (codes B18.0 and B18.2), obesity (code E66), and cardiovascular diseases including coronary artery disease (codes I20-I25), peripheral artery disease (code I702) and stroke (codes I63, I64). The annual prevalence of hospitalisation due to KD among PLHIV and the annual distribution of the various KD were then assessed. The changes in annual prevalence were determined for the study period (2008-2013).

In the second part of the study which aimed to assess the incidence of hospital admission due to KD in PLHIV, only PLHIV newly followed in 2009 were taken into account, whatever the duration of their first hospitalisation. Newly followed PLHIV were defined as

patients hospitalised with a diagnosis of HIV infection in 2009 but with no hospitalisation for HIV infection in the previous two years. We considered these patients as "newly followed PLHIV" because very few HIV patients in France had medical follow up outside the hospital setting during the study period. The newly followed PLHIV were monitored for five years, and all hospitalisations for KD were analysed along with any associated co-morbidities.

Changes over time in the proportion of PLHIV with KD were assessed using the Cochran Armitage Test, and changes in the number of patients in the HIV and KD cohorts were analysed with a Poisson model. We compared patient age in the AIDS defining-illness, non-AIDS HIV and the whole HIV cohorts with the t test, Mann Whitney test or Kruskall Wallis test. The characteristics of patients with and without AIDS were compared using Fisher's exact test and the chi-square test. Multivariable logistic regression and a Cox model were used to determine factors associated with a hospitalisation for incident KD. SAS statistical software (version 9.3) was used for all analyses.

Results

Patient characteristics

From 2008 to 2013, more than 5 million people were hospitalised each year in France. Their main characteristics over the study period are shown in **Table 1**. The proportion of patients hospitalized for KD rose progressively from 1.9% in 2008 to 2.4% in 2013 (p<0.01).

During the same period, an average of 10,862 PLHIV were hospitalised per year (**Table 2**). There was a significant decrease in the number of PLHIV admissions from 2010 to 2013 (P<0.01). There was also a significant increase in the mean age of these patients, from 45 years in 2008 to 48 years in 2013 (P<0.01).

The comorbidities known to be associated with an increased risk of KD in 2009 are presented in **Table 3**. Hepatic comorbidities were more frequently observed in hospitalised PLHIV (12.2% vs 0.3%), whereas all other comorbidities were more frequent in the general hospitalised population.

The distribution of hospitalisations for KD in PLHIV

Of the HIV infected patients admitted to hospital, 2,254 (3.5%) were hospitalised for at least 24 hours for KD during the 5-year study period **(Table 2)**. A significant increase was observed over time, from 3.0% in 2008 to 3.7% in 2013 (P < 0.01)**.** The HIV patients hospitalised for KD were significantly older than the overall HIV cohort (50 +/- 13 years vs 46 +/- 12 years, P < 0.01)**.**

The most common KDs upon admission were ARF (25.4%, [23.0-30.1%]), nephrolithiasis (22.1%, [20.2-24.0%] and pyelonephritis (22.1%, [15.9-26.8%]). The yearly proportion of patients hospitalised for ARF varied from 0.7% (n=77) to 1.0% (n=101) (0.9% on average, **Table 2**). Among hospitalisations for KD, the proportion of those linked to ARF remained stable over the study period (25.4% [23.0-30.1%]). The mean age of patients hospitalised with ARF was higher than the mean age of the whole cohort (51 +/- 13 years vs 46 +/- 12 years, P < 0.01). Hospitalisation for ARF was more often observed in AIDS patients than in PLHIV without AIDS (30.1% vs 21.2%, P < 0.01), the latter being older than the former

(55+/- 12 years vs 49+/- 12, P < 0.01). Hospitalisation for pyelonephritis was more common in AIDS patients, while the opposite was observed for nephrolithiasis

Other causes of hospitalisation for KD were renal parenchymal diseases (8.6%, [5.9-11.4%]), out of these glomerular diseases (6.4% of the hospitalisations for KD), with a roughly stable proportion throughout the study period. Of these glomerular diseases, 27% (n=48) were defined only by their glomerular syndrome, 25.2% (n=45) were defined via their association with another disease (such as infectious diseases, systemic disease and diabetes mellitus), and only 47.8% (n=85) were histologically assessed. The proportion of renal biopsies in AIDS PLHIV was similar to that in non-AIDS PLHIV (45.5% vs 37.6%, P=0.39). Of the histologically assessed glomerular diseases, FSGS was diagnosed in 37.6% of cases. While there was a non-significant upwards trend in the use of renal biopsy over the study period, the proportion of FSGS declined from 63.6% in 2008 to 27.3% in 2013. Other glomerular diseases were membranous nephropathy (14.1%, n=12), crescentic glomerulonephritis (12.9%, n=11), undetermined glomerulonephritis (10.6%, n=9), minimal change disease (9.4%, n=8) and membranoproliferative glomerulonephritis (7.1%, n=6). Mesangial proliferative glomerulonephritis and post-infectious glomerulonephritis were found in less than 5%. Tubulointerstitial disorders were infrequent (2.2%, n=49), decreasing from 3.3% in 2008 to 1% in 2013 (P=0.18). Drug-related tubulointerstitial or tubular injuries were the main cause of these hospitalisations (53.1%, n= 26).

Hospitalisations for KD in PLHIV newly followed in 2009

In 2009, 1113 PLHIV were newly followed, 66 of which were hospitalised for KD during the entire follow-up, which reveals a 5-year cumulative incidence of 5.9% **(Figure 1)**. Twenty-two (33.0%) of these patients were coded for KD at the initial hospitalisation or within one year.

Comorbidities in all newly followed PLHIV and in those hospitalised for KD are summarised in **Table 4.** In logistic analysis, factors associated with a higher risk of KD were age (OR = 1.02 [1.00-1.04]) and cardiovascular disease (OR=3.71 [1.18-11.67]). AIDS PLHIV was also associated in female patients (OR = 3.67 [1.26-10.70]). In survival analysis, cardiovascular disease remained significantly associated with the risk of KD (HR=3.39 [1.22-

9.42]). When focusing on female gender, AIDS PLHIV was also associated with this risk of KD (HR = 3.67 [1.26-10.70]).

Among the causes of incident KD requiring hospital admission, ARF was involved in 25 cases, and 66.7% of these occurred in the first two years of follow-up (50.0% in the first year and 16.7% in the second year). The 5-year cumulative incidence of ARF was 1.6%. No risk factor was significantly associated with the development of incident ARF requiring hospitalisation.

Discussion

Firstly, this study found that patients hospitalised for KD are 1.5 more frequent in PLHIV than in the general population. The rate of patients hospitalised increased steadily over time despite the fact that risk factors for KD are less frequent in PLHIV than in the general hospitalised population, except for hepatitis coinfections. These rates have increased significantly in recent years (from 3.0% in 2008 to 3.7% in 2013), albeit similar to the rates observed in the general population (5-year difference 0.7% vs 0.5%). ARF, nephrolithiasis and pyelonephritis accounted for more than three-quarters of hospital admissions for KD in our study. Glomerular or tubular diseases were rather infrequent but stable causes of hospitalisation. The most frequent glomerular disease was FSGS with 37.6% of histological codes, albeit with a downward trend since the beginning of the HAART era.

Another point is that ARF often occurs within 2 years following the diagnosis of HIV for the two-thirds of the newly diagnosed and followed PLHIV who subsequently presented ARF.

The last key finding is that nearly 6% of PLHIV were hospitalised for KD during the 5 years following the diagnosis of HIV infection, and that the risk was strongly associated with the presence of cardiovascular disease.

To our knowledge, this study is the first to focus on hospital admissions for KD in a large population of PLHIV. In our study, more than 10,850 PLHIV were hospitalised each year, i.e. about 10% of the estimated cohort of 110,900 PLHIV medically followed-up in 2010 in France. The exhaustive nature of our data ensures that the results are representative of all hospitalisations for KD in France, which is particularly important for both HIV and kidney disease which can be influenced by the ethnic origins of the population

This study is the first to show such a trend in a nationwide setting, and is consistent with other studies that have reported hospitalisations rates for KD ranging from 2.6% to 3.3% [19].

The proportion of FSGS at the beginning of our study (63.6% in 2008) is similar to that reported in other studies [13 20 21], and the trend towards a decrease in the percentage we observed (27.3% in 2013) was also reported in another recent study (28%) [22].

ARF was responsible for approximately 1% of in hospitalised PLHIV, a rate which is lower than that observed in the few previous studies focusing on PLHIV (2.8 to 5.9 per 100 patient years [3 4 23]. The most likely explanation is that we only considered ARF cases leading to hospitalisation, and not all ARF, including those occurring in inpatients hospitalised for other reasons (e.g. sepsis or volume depletion). For example, 31% (34/111) of patients in the study by Franceschini *et al.* developed ARF during a hospital stay, and 38% had community-acquired ARF not requiring hospitalisation [24]. Furthermore, we also did not consider ARF in PLHIV hospitalised for CKD. This also probably explains why many studies reported ARF hospitalisation rates that were 3 or 4 times higher in PLHIV than in the general population, whereas we observed an ARF hospitalisation rate in PLHIV close to that observed in the general population (0.6 to 1%) [25 26]. Nonetheless, ARF remains a concern in PLHIV as the average age at the time of hospitalisation is lower than that in the general population.

Our study has several limitations, the main one being the use of administrative codes. However, these codes are based on the clinical judgment of physicians and laboratory values. The use of this type of database has been validated for KD [27 28] and particularly for ARF [27 28]. In addition, the infrequent use of renal biopsies precluded an extended analysis of parenchymental KD leading to hospitalisation, and we do not distinguish HIVAN from HIVICK. Finally, it was not possible to provide accurate characteristics of the HIV infection in the absence of data on HIV viral load or CD4 cell count, and/or on the antiretroviral drugs used. Nonetheless, the aim of our study was to provide an overview of kidney disease in PLHIV. Other studies are necessary to extend the available data about each kidney condition in PLHIV.

FSGS, which is probably represented by HIVAN, is still the most frequent nephropathy in PLHIV though it has decreased relative to other glomerulopathies following the expansion of HAART (13,15). Nevertheless, nearly 60% of our PLHIV cohort hospitalised for glomerular disease were not biopsied. Almost 50% of these patients had proteinuria or nephrotic syndrome (3.4% and 44.4%, respectively). These figures reveal a gap between the proportion of glomerular diseases and the number of renal biopsies performed. Several studies have confirmed the importance of performing kidney biopsies in PLHIV [22 29]. Radiological examinations, urinary findings, renal function biological and proteinuria evaluations do not provide sufficiently specific information to diagnose HIV-related nephropathy [29 30]. Much like

U.S. guidelines from 2014 [4], the French guidelines [31] recommend referring patients to a nephrologist if the eGFR falls to less than 60 ml/min and/or as soon as proteinuria appears. The U.S. recommendations also suggest that biopsies should be done in HIV-infected patients in whom a definitive diagnosis may affect management or inform the prognosis [4].

ARF often occurs early during follow-up [32 33] with a 10-fold higher rate of ARF in the first 3 months after the introduction of HAART [32], probably reflecting the disease burden in PLHIV with more advanced HIV disease and concurrent infections at the time of admission [32 33]. Indeed, opportunistic infections may play an important role in the development of early onset ARF.

By contrast, associated comorbidities and HAART toxicity are important factors leading to "late-onset ARF" [32], as suggested by the older age of non-AIDS PLHIV experiencing ARF. This can probably be explained by the pathophysiological link between some comorbidities such a cardiovascular diseases and KD, that has also been reported in PLHIV [34-36]. Since cardiovascular comorbidity is particularly frequent in PLHIV [37], it should be closely monitored and managed to prevent serious KD.

In conclusion, the proportion of PLHIV hospitalised for ARF and other types of KD remains significant and has not decreased despite the increasing use of HAART. PLHIV must be considered a high-risk population for KD, particularly for those with simultaneous cardiovascular disease. ARF remains the leading cause of hospitalisation for renal disorders, which essentially occur early during the follow-up, suggesting the need for regular and specific follow-up, at least during the first year. Glomerular and tubular diseases, which were also stable over time, should be documented more often by biopsies, whose results can inform the clinicians who treat these diseases, and improve prognostic outcomes. All of these data reflect changes in the impact of HIV infection, comorbidities and treatments, and underline the need to regularly address this issue in the future.

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Table 1: *General patient population characteristics and distribution of KD and ARF hospital admissions, per year*

General population	2008	2009	2010	2011	2012	2013	Mean
Number of patients hospitalised (n, all causes)	5287364	5232412	5170695	5193430	5217264	5163969	5210856
Sex ratio (M/F)	47.3% / 52.7%	48.1% / 51.9%	48.0% / 52.0%	47.9% / 52.1%	47.7% / 52.3%	47.8% / 52.2%	47.8% / 52.2%
Age (mean, years)	59 +/- 20	59 +/- 20	60 +/- 20	60 +/- 20	60 +/- 20	61 +/- 20	60+/-20
Number of patients hospitalised (for more than 24 hours for kidney disease, n ,% general population)	102420 (1.9%)	106853 (2.0%)	109931 (2.1%)	113492 (2.2%)	118000 (2.3%)	122515 (2.4%)	112202 (2.2%)
Sex ratio (M/F)	53.0% / 47.0%	52.9% / 47.1%	52.7% / 47.3%	52.7% / 47.3%	52.6% / 47.4%	52.4% / 47.6%	52.7%/47.3%
Age (mean, years)	64 +/- 18	64 +/- 18	65 +/- 18	65 +/- 18	65 +/- 18	66 +/- 18	65+/-18
Number of patients hospitalised (for more than 24 hours for ARF , n, % of general population)	15993 (0.3%)	17473 (0.3%)	16567 (0.3%)	16491 (0.3%)	17082 (0.3%)	17478 (0.3%)	16847 (0.3%)
Sex ratio (M/F)	59.2% / 40.8%	58.5% / 41.5%	59.6% / 40.4%	59.2% / 40.8%	59.4% / 40.6%	59.6% / 40.4%	59.3%/40.7%
Age (mean, years)	71 +/- 15	71 +/- 15	71 +/-15	71 +/- 15	71 +/- 14	71+/- 15	71+/- 15

Table 2: *General characteristics of PLHIV and distribution of KD and ARF hospitalisations, per year*

People living with HIV	2008	2009	2010	2011	2012	2013	Mean
Number of patients hospitalised (n, all causes)	10 878	11 418	11226	10 638	10 568	10 445	**10 862**
Sex ratio (M/F)	61.3% / 38.7%	61.1% / 38.9%	60.9% / 39.1%	62.0% / 38.0%	61.7% / 38.3%	62.5% / 36.5%	**61.6% /38.4%**
Age (mean, years)	45 +/- 12	45 +/- 12	46 +/- 12	47 +/- 12	47 +/- 12	48 +/- 13	**46+/-12**
AIDS-defining illness stage (n, %)	4204 (38.6%)	4302 (37.7%)	4403 (39.2%)	4005 (37.6%)	3865 (36.6%)	3692 (35.3%)	**4124 (37.5%)**
Number of patients hospitalised (longer than 24 hours for KD, n ,% of hospitalised HIV positive patients)	330 (3.0%)	396 (3.5%)	365 (3.3%)	378 (3.6%)	396 (3.7%)	389 (3.7%)	**376 (3.5%)**
Sex ratio (M/F)	60.6% / 39.4%	61.4% / 38.6%	65.2% / 34.8%	62.2% / 37.8%	58.6% / 41.4%	60.7% / 39.3%	**61.4%/ 38.6%**
Age (mean, years)	48 +/- 12	50 +/- 13	51 +/- 13	49 +/- 13	52 +/- 13	52 +/- 13	**50+/-13**
AIDS-defining illness stage (n, %)	159 (48.2%)	178 (44.9%)	180 (49.3%)	184 (48.7%)	178 (44.9%)	180 (46.3%)	**177 (47.0%)**
Number of patients hospitalised (longer than 24 hours for ARF , n, % of hospitalised HIV positive patients)	77 (0.7%)	105 (0.9%)	110 (1.0%)	87 (0.8%)	92 (0.9%)	101 (1.0%)	**95 (0.9%)**
Sex ratio (M/F)	74.0% / 26.0%	70.5% / 29.5%	71.8% / 28.2%	71.3% / 28.7%	80.4% / 19.6%	74.3% / 25.7%	**73.6%/26.4%**
Age (mean, years)	48 +/- 11	50 +/- 13	50 +/-12	50 +/- 12	55 +/- 12	55 +/- 13	**51+/- 13**
AIDS-defining illness stage (n, %)	41 (53.2%)	57 (54.3%)	64 (58.2%)	53 (60.9%)	46 (50.0%)	58 (57.4%)	**53 (55.8%)**

Table 3: *Comorbidities in the hospitalised general population and hospitalised HIV population for the year 2009*

Comorbidities	General population n=5232412	HIV n=11418	p-value
Hepatitis co-infections* , n, %	16390 (0.3%)	1397 (12.2%)	<0.01
Hypertension, n, %	1136018 (21.7%)	927 (8.1%)	<0.01
Diabetes mellitus, n, %	526511 (10.1%)	651 (5.7%)	<0.01
Cardiovascular diseases¥, n, %	683316 (13.1%)	821 (7.2%)	<0.01
Dyslipidaemia, n, %	375600 (7.2%)	425 (3.7%)	<0.01
Obesity, n, %	282517 (5.4%)	229 (3.0%)	<0.01
Heart failure, n, %	218697 (4.2%)	151 (1.3%)	<0.01

**Hepatitis co-infections included hepatitis C and/or hepatitis B*

¥ Cardiovascular diseases included coronary artery diseases, peripheral artery disease and stroke.

Table 4: *Comorbidities in all newly followed PLHIV and in those hospitalised for KD*

Comorbidities	Total newly followed PLHIV n=1113	Newly followed PLHIV with KD n=66	*P*
Hepatitis co-infections , n, %	89 (8.0%)	4 (6.1%)	*0.55*
Hypertension, n, %	53 (4.8%)	5 (7.6%)	*0.24*
Mellitus diabetes, n, %	37 (3.3%)	2 (3.0%)	*1.00*
Cardiovascular diseases¥, n, %	28 (2.5%)	5 (7.6%)	*0.03*
Dyslipidaemia, n, %	11 (1.0%)	1 (1.5%)	*0.49*
Obesity, n, %	14 (1.3%)	2 (3.0%)	*0.20*
Heart failure, n, %	5 (0.4%)	1 (1.5%)	-

**Hepatitis co-infections including hepatitis C and/or hepatitis B*

¥ Cardiovascular diseases included coronary artery diseases, peripheral artery disease and stroke.

Figure 1: *Cumulative incidence of KD requiring hospitalisation for all newly followed PLHIV (grey curve), for those without past or present AIDS (light bars) and for those with past or present AIDS-defining illness (dark bars).*

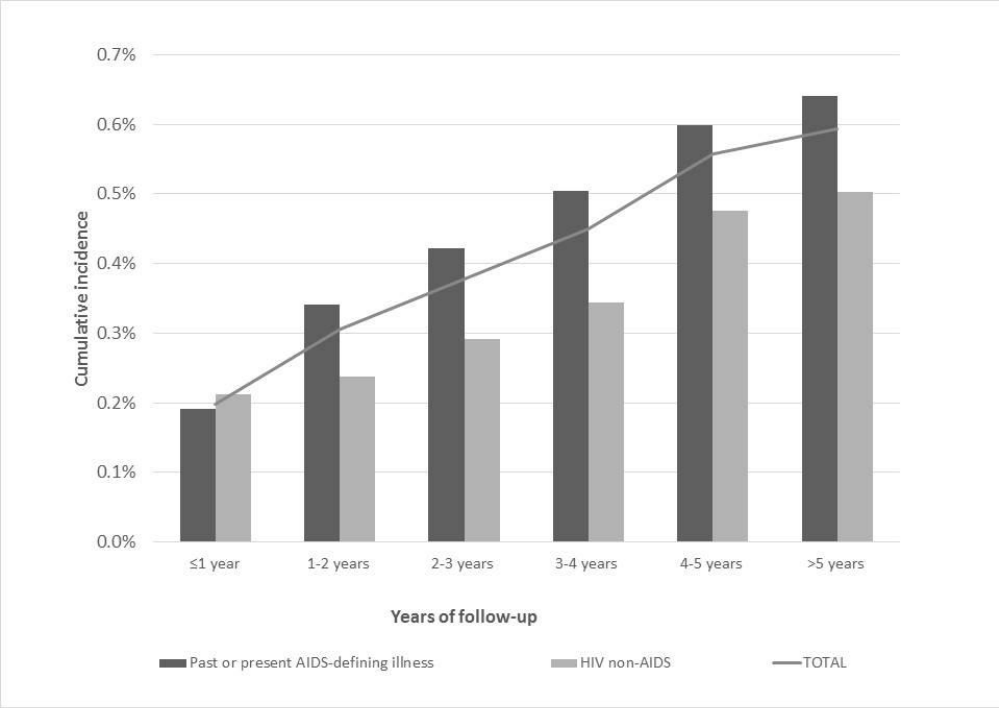

Figure 1: Cumulative incidence of KD requiring hospitalisation for all newly followed PLHIV (grey curve), for those without past or present AIDS (light bars) and for those with past or present AIDS-defining illness (dark bars).

81x60mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
7Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10-tables
		(*b*) Report category boundaries when continuous variables were categorized	8-10-tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-10-tables
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Prevalence and incidence of kidney diseases leading to hospital admission in people living with HIV in France: an observational nationwide study

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Prevalence and incidence of kidney diseases leading to hospital admission in people living with HIV in France: an observational nationwide study

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Patient and Public Involvement this study used an anonymized database, patients were thus not involved.

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Data sharing statement The PMSI database was transmitted by the national agency for the management of hospitalization data. The use of these data by our department was approved by the National Committee for data protection. We are not allowed to transmit these data.

Abstract (294 words)

Objectives: To describe hospitalisations for kidney disease (KD) among persons living with HIV (PLHIV) in France and to identify the factors associated with such hospitalisations since data on the epidemiology of KD leading to hospitalisation are globally scarce.

Design: Observational nationwide study using the French PMSI (Programme de Médicalisation des Systèmes d'Information) database.

Setting: France 2008-2013

Participants: Around 10,862 PLHIV out of a mean of 5,210,856 patients hospitalised each year. All hospital admissions with a main diagnosis code indicating KD (ICD-10 codes N00 to N39) were collected.

Main outcome measures: The prevalence and incidence of KD leading to hospital admission in PLHIV and the associated risk factors..

Results: The prevalence of patients hospitalised for KD was 1.5 higher in PLHIV than in the general population, and increased significantly from 3.0% in 2008 to 3.7% in 2013 ($P < 0.01$). The main cause of hospitalisation for KD was acute renal failure (ARF, 25.4%). Glomerular diseases remained stable (6.4%) throughout the study period, focal segmental glomerulosclerosis being the main diagnosis (37.6%). Only 41.3% of patients hospitalised for glomerular disease were biopsied. The other common motives for admission were nephrolithiasis (22.1%) and pyelonephritis (22.6%).

The 5-year cumulative incidence of KD requiring hospitalisation was 5.9% in HIV patients newly diagnosed for HIV in 2009. Factors associated with a higher risk of incident KD requiring hospitalisation were cardiovascular disease (HR=3.30, 1.46 to 7.49), and, for female patients, AIDS (HR=2.45, 1.07 to 5.58). Two thirds of hospitalisations for incident ARF occurred in the first two years of follow-up.

Conclusions: Hospital admission for KD is more frequent in PLHIV than in the general population and increases over time. ARF remains the leading cause. Glomerular diseases are infrequently documented by renal biopsies. Older patients and those with cardiovascular disease are particularly concerned.

Strengths and limitations of this study

- This study is the first to focus on hospital admissions for kidney disease (KD) in a large population people living with HIV (PLHIV).
- The exhaustive nature of our data ensures that the results are representative of all hospitalisations for KD in France.
- The main limitation is the use of administrative codes, even though they are based on the clinical judgment of physicians and on laboratory values.
- It was also not possible to provide accurate characteristics of the HIV infection

Keywords: HIV; kidney disease; acute renal failure; glomerular disease; hospitalisation

Introduction

In 2015, 36.9 million people around the world and about 130,000 in France were living with HIV. The introduction of highly active antiretroviral therapy (HAART) has dramatically decreased mortality and significantly improved the quality of life of people living with HIV (PLHIV). However, an increase in the incidence of co-morbidities, including kidney disease (KD), has been observed [1 2]. Several studies have shown that acute renal failure (ARF) was three to four times more frequent in PLHIV than in the general population [3 4] and that its incidence did not decrease as HAART became more common [5]. ARF, in the general population and PLHIV, has also been associated with longer hospital stays and higher costs, and with a risk of progression to chronic KD (CKD) [6-8].

The incidence of CKD is reportedly higher in PLHIV than in people not infected with HIV [9]. Its prevalence has been estimated at between 1% in the D.A.D study [10] and 4.9% in a French cohort of 2,588 patients [11]. The proportion of HIV-associated nephropathy (HIVAN) has significantly fallen [12], while that of other KDs, such as classical focal segmental glomerulosclerosis (FSGS) or HIV-associated immune complex KD (HIVICK), has increased [13]. The increase in the incidence of CKD could also be related to the nephrotoxicity of some antiretroviral drugs or to the increased frequency of co-morbidities, such as diabetes, hypertension, cardiovascular disease, or hepatitis C or B coinfection [6 10 14].

However, to our knowledge, no studies have dealt with the epidemiology of KD leading to hospitalisation in PLHIV in the recent HAART era. We thus conducted a national observational study to describe hospital admissions for KD in PLHIV in France and to identify factors associated with such admissions.

Patients and Methods

This study was an observational retrospective multicentre study based on nationwide PMSI (Programme de Médicalisation des Systèmes d'Information) data from 2008 to 2013. The French PMSI database is similar to the Medicare database and includes all admissions in all hospitals from 1997 onwards. Since 2007, it has been possible to link all discharge abstracts for a single patient. Diagnoses identified during hospital stays are coded according to the tenth edition of the International Classification of Diseases (ICD-10). This database

provides a vast amount of epidemiological information regarding hospitalised patients in France [15-18], is truly representative, and can be used to detect rare events.

In the first part of the study, all patients older than 18 years hospitalised with a main or associated diagnosis of HIV infection (ICD-10 code B20-24, Z21) were eligible. All patients with at least one hospitalisation lasting more than 24 hours were included. Those hospitalised for less than 24 hours were excluded since repeated short hospitalisations were most often regular follow-up consultations or ambulatory care. Age, sex, comorbidities and patient outcomes in the year following hospitalisation were collected. Each patient was classified as having past or present AIDS-defining illness (Centers for Disease Control (CDC) Stage C, codes B20-22, B241) or being HIV infected without progression to AIDS (CDC stages A and B, codes B23, B240, B249, and Z21). Hospital admissions with a main diagnosis code corresponding to KD (ICD-10 codes N00 to N39) in the year following the first hospitalisation with a diagnosis of HIV infection were collected. The KDs were defined and classified as follows: acute renal failure (codes N17 and 19), chronic KD either at first diagnosis or with associated complications, acute renal failure (code N18), nephrolithiasis (codes N13, 20, 21, 22 and 23), pyelonephritis (codes N10, 11, 12 and 15), renal parenchymal diseases (including glomerular and tubular diseases) (codes N01-06, N08, N14, N16 and N25), and other KD (codes N26, 27, 28, 29 and N39). For glomerular diseases, both the syndrome (e.g. nephrotic syndrome) and the related disease (e.g. membranous nephropathy) were available. The identified syndromes were haematuria, proteinuria, nephrotic syndrome, and acute or chronic nephritic syndrome. Comorbidities were also collected: hypertension (codes I10-I15), diabetes mellitus (codes E10-E14), dyslipidaemia (code E78), heart failure (code I50), coinfection with hepatitis B and / or hepatitis C (codes B18.0 and B18.2), obesity (code E66), and cardiovascular diseases including coronary artery disease (codes I20-I25), peripheral artery disease (code I702) and stroke (codes I63, I64). The annual prevalence of hospitalisation due to KD among PLHIV and the annual distribution of the various KD were then assessed. The changes in annual prevalence were determined for the study period (2008-2013).

In the second part of the study which aimed to assess the incidence of hospital admission due to KD in PLHIV, only PLHIV newly followed in 2009 were taken into account, whatever the duration of their first hospitalisation. Newly followed PLHIV were defined as

patients hospitalised with a diagnosis of HIV infection in 2009 but with no hospitalisation for HIV infection in the previous two years. We considered these patients as "newly followed PLHIV" because very few HIV patients in France had medical follow up outside the hospital setting during the study period. The newly followed PLHIV were monitored for five years, and all hospitalisations for KD were analysed along with any associated co-morbidities.

For all analyses, patients who were hospitalised several times for KD were only considered once. Changes over time in the proportion of PLHIV with KD were assessed using the Cochran Armitage Test, and changes in the number of patients in the HIV and KD cohorts were analysed with a Poisson model. We compared patient age in the AIDS defining-illness, non-AIDS HIV and the whole HIV cohorts with the t test, Mann Whitney test or Kruskall Wallis test. The characteristics of patients with and without AIDS were compared using Fisher's exact test and the chi-square test. A Cox model was used to determine factors associated with a hospitalisation for incident KD, with a follow-up of 5 years. Individuals were censored at death, at the end of the follow-up or the latest all-cause hospitalisation for people without KD. In multivariate analyses, we introduced all the variables considered significant in the univariate analyses ($p<0.20$) and according to their clinical relevance. We have therefore included: age, gender, having past or present AIDS-defining illness, obesity, co-infection, dyslipidaemia, HTA, diabetes and cardiovascular diseases in the multivariate analyses. The proportional hazards assumption was assessed for each variable and interaction tested. To limit sparse-data bias [19], we performed two penalisation estimations: the first one using the Firth bias adjustment [20] and the second one using data augmentation [21]. SAS statistical software (version 9.3) was used for all analyses.

Results

Patient characteristics

From 2008 to 2013, more than 5 million people were hospitalised each year in France. Their main characteristics over the study period are shown in **Table 1**. The proportion of patients hospitalized for KD rose progressively from 1.9% in 2008 to 2.4% in 2013 (p<0.0001).

During the same period, an average of 10,862 PLHIV were hospitalised per year (**Table 2**). There was a significant decrease in the number of PLHIV admissions from 2010 to 2013 (p<0.0001). There was also a significant increase in the mean age of these patients, from 45 years in 2008 to 48 years in 2013.

Since the mean proportion of patients hospitalized for KD was globally 2.2% in the general population **(Table 1)** and 3.5% in PLHIV **(Table 2)**, the prevalence of admission for KD in PLHIV was 1.5 higher than in the general population.

The comorbidities known to be associated with an increased risk of KD in 2009 are presented in **Table 3**. Hepatic comorbidities were more frequently observed in hospitalised PLHIV (12.2% vs 0.3%), whereas all other comorbidities were more frequent in the general hospitalised population.

The distribution of hospitalisations for KD in PLHIV

Of the HIV infected patients admitted to hospital, 2,254 (3.5%) were hospitalised for at least 24 hours for KD during the 5-year study period **(Table 2)**. A significant increase was observed over time, from 3.0% in 2008 to 3.7% in 2013 (p=0.0019)**.** The HIV patients hospitalised for KD were significantly older than the overall HIV cohort (50 +/- 13 years vs 46 +/- 12 years, p<0.01)**.**

The most common KDs upon admission were ARF (25.4%, [23.0-30.1%]), nephrolithiasis (22.1%, [20.2-24.0%] and pyelonephritis (22.1%, [15.9-26.8%]). The yearly proportion of patients hospitalised for ARF varied from 0.7% (n=77) to 1.0% (n=101) (0.9% on average, **Table 2**). Among hospitalisations for KD, the proportion of those linked to ARF remained stable over the study period (25.4% [23.0-30.1%]). The mean age of patients

hospitalised with ARF was higher than the mean age of the whole cohort (51 +/- 13 years vs 46 +/- 12 years). Hospitalisation for ARF was more often observed in AIDS patients than in PLHIV without AIDS (30.1% vs 21.2%), the latter being older than the former (55+/- 12 years vs 49+/- 12). Hospitalisation for pyelonephritis was more common in AIDS patients, while the opposite was observed for nephrolithiasis

Other causes of hospitalisation for KD were renal parenchymal diseases (8.6%, [5.9-11.4%]), out of these glomerular diseases (6.4% of the hospitalisations for KD), with a roughly stable proportion throughout the study period. Of these glomerular diseases, 27% (n=48) were defined only by their glomerular syndrome, 25.2% (n=45) were defined via their association with another disease (such as infectious diseases, systemic disease and diabetes mellitus), and only 47.8% (n=85) were histologically assessed. The proportion of renal biopsies in AIDS PLHIV was similar to that in non-AIDS PLHIV (45.5% vs 37.6%). Of the histologically assessed glomerular diseases, FSGS was diagnosed in 37.6% of cases. While there was a non-significant upwards trend in the use of renal biopsy over the study period, the proportion of FSGS declined from 63.6% in 2008 to 27.3% in 2013. Other glomerular diseases were membranous nephropathy (14.1%, n=12), crescentic glomerulonephritis (12.9%, n=11), undetermined glomerulonephritis (10.6%, n=9), minimal change disease (9.4%, n=8) and membranoproliferative glomerulonephritis (7.1%, n=6). Mesangial proliferative glomerulonephritis and post-infectious glomerulonephritis were found in less than 5%. Tubulointerstitial disorders were infrequent (2.2%, n=49), decreasing from 3.3% in 2008 to 1% in 2013 (P=0.18). Drug-related tubulointerstitial or tubular injuries were the main cause of these hospitalisations (53.1%, n= 26).

Hospitalisations for KD in PLHIV newly followed in 2009

Comorbidities in all newly followed PLHIV and in those hospitalised for KD are summarised in **Table 4.**

In 2009, 1113 PLHIV were newly followed, 66 of which were hospitalised for KD during the entire follow-up, which reveals a 5-year cumulative incidence of 5.9% **(Figure 1)**. Twenty-two (33.0%) of these patients were coded for KD at the initial hospitalisation or within one year.

The median of follow-up time was 843 days with an interquartile range of 1,459 days. As there was an interaction between having past or present AIDS-defining illness, or not, and gender, Kaplan-Meier curves and the associated log-rank tests for each gender are presented in **Figures 2A and 2B**. For women, the risk of KD was higher for those having past or present AIDS-defining illness than those who did not (p=0.0127). In multivariate survival analysis (**Table 5**), cardiovascular disease was significantly associated with the risk of KD (HR=3.39 [1.22-9.42]). When focusing on female gender, having past or present AIDS-defining illness remained associated with this risk of KD (HR = 3.67 [1.26-10.70]). As our confidence intervals were wide with huge upper 95% limits (greater about 10), we performed two penalization estimations: the first one using the Firth bias adjustment and the second one using data augmentation. With the Firth bias adjustment, we observed a slight decrease of the upper 95% limits, while with the penalisation by data augmentation, these limits were widely reduced with a HR=3.30 [1.46-7.49] for cardiovascular disease and a HR=2.45 [1.07-5.58] for female gender having past or present AIDS-defining illness (**Table 5**).

Among the causes of incident KD requiring hospital admission, ARF was involved in 25 cases, and 66.7% of these occurred in the first two years of follow-up (50.0% in the first year and 16.7% in the second year). The 5-year cumulative incidence of ARF was 1.6%. No risk factor was significantly associated with the development of incident ARF requiring hospitalisation.

Discussion

Firstly, this study found that patients hospitalised for KD are 1.5 more frequent in PLHIV than in the general population. The rate of patients hospitalised increased steadily over time despite the fact that risk factors for KD are less frequent in PLHIV than in the general hospitalised population, except for hepatitis coinfections. These rates have increased significantly in recent years (from 3.0% in 2008 to 3.7% in 2013), albeit similar to the rates observed in the general population (5-year difference 0.7% vs 0.5%). ARF, nephrolithiasis and pyelonephritis accounted for more than three-quarters of hospital admissions for KD in our study. Glomerular or tubular diseases were rather infrequent but stable causes of hospitalisation. The most frequent glomerular disease was FSGS with 37.6% of histological codes, albeit with a downward trend since the beginning of the HAART era.

Another point is that ARF often occurs within 2 years following the diagnosis of HIV for the two-thirds of the newly diagnosed and followed PLHIV who subsequently presented ARF.

The last key finding is that nearly 6% of PLHIV were hospitalised for KD during the 5 years following the diagnosis of HIV infection, and that the risk was strongly associated with the presence of cardiovascular disease.

To our knowledge, this study is the first to focus on hospital admissions for KD in a large population of PLHIV. In our study, more than 10,850 PLHIV were hospitalised each year, i.e. about 10% of the estimated cohort of 110,900 PLHIV medically followed-up in 2010 in France. The exhaustive nature of our data ensures that the results are representative of all hospitalisations for KD in France, which is particularly important for both HIV and kidney disease which can be influenced by the ethnic origins of the population

This study is the first to show such a trend in a nationwide setting, and is consistent with other studies that have reported hospitalisations rates for KD ranging from 2.6% to 3.3% [22].

The proportion of FSGS at the beginning of our study (63.6% in 2008) is similar to that reported in other studies [13 23 24], and the trend towards a decrease in the percentage we observed (27.3% in 2013) was also reported in another recent study (28%) [25].

ARF was responsible for approximately 1% of in hospitalised PLHIV, a rate which is lower than that observed in the few previous studies focusing on PLHIV (2.8 to 5.9 per 100 patient years [3 4 26]. The most likely explanation is that we only considered ARF cases leading to hospitalisation, and not all ARF, including those occurring in inpatients hospitalised for other reasons (e.g. sepsis or volume depletion). For example, 31% (34/111) of patients in the study by Franceschini *et al.* developed ARF during a hospital stay, and 38% had community-acquired ARF not requiring hospitalisation [27]. Furthermore, we also did not consider ARF in PLHIV hospitalised for CKD. This also probably explains why many studies reported ARF hospitalisation rates that were 3 or 4 times higher in PLHIV than in the general population, whereas we observed an ARF hospitalisation rate in PLHIV close to that observed in the general population (0.6 to 1%) [28 29]. Nonetheless, ARF remains a concern in PLHIV as the average age at the time of hospitalisation is lower than that in the general population.

Our study has several limitations, the main one being the use of administrative codes. However, these codes are based on the clinical judgment of physicians and laboratory values. The use of this type of database has been validated for KD [30 31] and particularly for ARF [30 31]. In addition, the infrequent use of renal biopsies precluded an extended analysis of parenchymental KD leading to hospitalisation, and we do not distinguish HIVAN from HIVICK. Finally, it was not possible to provide accurate characteristics of the HIV infection in the absence of data on HIV viral load or CD4 cell count, and/or on the antiretroviral drugs used. Nonetheless, the aim of our study was to provide an overview of kidney disease in PLHIV. Moreover, our high hazard ratios and wide confidence intervals could be a sign of sparse-data bias, which may be due to our small number of events. However, after performing penalised estimation such as Firth bias adjustment or penalisation by data augmentation, we were able to reduce our upper 95% limits while maintaining the significance of our different factors.

Other studies are necessary to extend the available data about each kidney condition in PLHIV.

FSGS, which is probably represented by HIVAN, is still the most frequent nephropathy in PLHIV though it has decreased relative to other glomerulopathies following the expansion of HAART (13,15). Nevertheless, nearly 60% of our PLHIV cohort hospitalised for glomerular

disease were not biopsied. Almost 50% of these patients had proteinuria or nephrotic syndrome (3.4% and 44.4%, respectively). These figures reveal a gap between the proportion of glomerular diseases and the number of renal biopsies performed. Several studies have confirmed the importance of performing kidney biopsies in PLHIV [25] [32]. Radiological examinations, urinary findings, renal function biological and proteinuria evaluations do not provide sufficiently specific information to diagnose HIV-related nephropathy [32] [33]. Much like U.S. guidelines from 2014 [4], the French guidelines [34] recommend referring patients to a nephrologist if the eGFR falls to less than 60 ml/min and/or as soon as proteinuria appears. The U.S. recommendations also suggest that biopsies should be done in HIV-infected patients in whom a definitive diagnosis may affect management or inform the prognosis [4].

ARF often occurs early during follow-up [35] [36] with a 10-fold higher rate of ARF in the first 3 months after the introduction of HAART [35], probably reflecting the disease burden in PLHIV with more advanced HIV disease and concurrent infections at the time of admission [35] [36]. Indeed, opportunistic infections may play an important role in the development of early onset ARF.

By contrast, associated comorbidities and HAART toxicity are important factors leading to "late-onset ARF" [35], as suggested by the older age of non-AIDS PLHIV experiencing ARF. This can probably be explained by the pathophysiological link between some comorbidities such a cardiovascular diseases and KD, that has also been reported in PLHIV [37-39]. Since cardiovascular comorbidity is particularly frequent in PLHIV [40], it should be closely monitored and managed to prevent serious KD.

In conclusion, the proportion of PLHIV hospitalised for ARF and other types of KD remains significant and has not decreased despite the increasing use of HAART. PLHIV must be considered a high-risk population for KD, particularly for those with simultaneous cardiovascular disease. ARF remains the leading cause of hospitalisation for renal disorders, which essentially occur early during the follow-up, suggesting the need for regular and specific follow-up, at least during the first year. Glomerular and tubular diseases, which were also stable over time, should be documented more often by biopsies, whose results can inform the clinicians who treat these diseases, and improve prognostic outcomes. All of

these data reflect changes in the impact of HIV infection, comorbidities and treatments, and underline the need to regularly address this issue in the future.

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Table 1: *General patient population characteristics and distribution of KD and ARF hospital admissions, per year*

General population	2008	2009	2010	2011	2012	2013	Mean
Number of patients hospitalised (n, all causes)	5287364	5232412	5170695	5193430	5217264	5163969	5210856
Sex ratio (M/F)	47.3% / 52.7%	48.1% / 51.9%	48.0% / 52.0%	47.9% / 52.1%	47.7% / 52.3%	47.8% / 52.2%	47.8% / 52.2%
Age (mean, years)	59 +/- 20	59 +/- 20	60 +/- 20	60 +/- 20	60 +/- 20	61 +/- 20	60+/-20
Number of patients hospitalised (for more than 24 hours for kidney disease, n ,% general population)	102420 (1.9%)	106853 (2.0%)	109931 (2.1%)	113492 (2.2%)	118000 (2.3%)	122515 (2.4%)	112202 (2.2%)
Sex ratio (M/F)	53.0% / 47.0%	52.9% / 47.1%	52.7% / 47.3%	52.7% / 47.3%	52.6% / 47.4%	52.4% / 47.6%	52.7%/47.3%
Age (mean, years)	64 +/- 18	64 +/- 18	65 +/- 18	65 +/- 18	65 +/- 18	66 +/- 18	65+/-18
Number of patients hospitalised (for more than 24 hours for ARF , n, % of general population)	15993 (0.3%)	17473 (0.3%)	16567 (0.3%)	16491 (0.3%)	17082 (0.3%)	17478 (0.3%)	16847 (0.3%)
Sex ratio (M/F)	59.2% / 40.8%	58.5% / 41.5%	59.6% / 40.4%	59.2% / 40.8%	59.4% / 40.6%	59.6% / 40.4%	59.3%/40.7%
Age (mean, years)	71 +/- 15	71 +/- 15	71 +/-15	71 +/- 15	71 +/- 14	71+/- 15	71+/- 15

The proportion of patients hospitalised for KD rose progressively from 1.9% in 2008 to 2.4% in 2013: Cochran-Armitage test, p<0.0001

Table 2: *General characteristics of PLHIV and distribution of KD and ARF hospitalisations, per year*

People living with HIV	2008	2009	2010	2011	2012	2013	Mean
Number of patients hospitalised (n, all causes)	10 878	11 418	11226	10 638	10 568	10 445	**10 862 ***
Sex ratio (M/F)	61.3% / 38.7%	61.1% / 38.9%	60.9% / 39.1%	62.0% / 38.0%	61.7% / 38.3%	62.5% / 36.5%	**61.6% /38.4%**
Age (mean, years)	45 +/- 12	45 +/- 12	46 +/- 12	47 +/- 12	47 +/- 12	48 +/- 13	**46+/-12**
AIDS-defining illness stage (n, %)	4204 (38.6%)	4302 (37.7%)	4403 (39.2%)	4005 (37.6%)	3865 (36.6%)	3692 (35.3%)	**4124 (37.5%)**
Number of patients hospitalised (longer than 24 hours for KD, n ,% of hospitalised HIV positive patients)	330 (3.0%)	396 (3.5%)	365 (3.3%)	378 (3.6%)	396 (3.7%)	389 (3.7%)	**376 (3.5%) ****
Sex ratio (M/F)	60.6% / 39.4%	61.4% / 38.6%	65.2% / 34.8%	62.2% / 37.8%	58.6% / 41.4%	60.7% / 39.3%	**61.4%/ 38.6%**
Age (mean, years)	48 +/- 12	50 +/- 13	51 +/- 13	49 +/- 13	52 +/- 13	52 +/- 13	**50+/-13**
AIDS-defining illness stage (n, %)	159 (48.2%)	178 (44.9%)	180 (49.3%)	184 (48.7%)	178 (44.9%)	180 (46.3%)	**177 (47.0%)**
Number of patients hospitalised (longer than 24 hours for ARF , n, % of hospitalised HIV positive patients)	77 (0.7%)	105 (0.9%)	110 (1.0%)	87 (0.8%)	92 (0.9%)	101 (1.0%)	**95 (0.9%)**
Sex ratio (M/F)	74.0% / 26.0%	70.5% / 29.5%	71.8% / 28.2%	71.3% / 28.7%	80.4% / 19.6%	74.3% / 25.7%	**73.6%/26.4%**
Age (mean, years)	48 +/- 11	50 +/- 13	50 +/-12	50 +/- 12	55 +/- 12	55 +/- 13	**51+/- 13**
AIDS-defining illness stage (n, %)	41 (53.2%)	57 (54.3%)	64 (58.2%)	53 (60.9%)	46 (50.0%)	58 (57.4%)	**53 (55.8%)**

* There was a significant decrease in the number of PLHIV admissions from 2010 to 2013: Poisson model, p<0.0001

** A significant increase of the proportion of patients hospitalized for KD was observed over time, from 3.0% in 2008 to 3.7% in 2013: Cochran-Armitage test, p=0.0019

Table 3: *Comorbidities in the hospitalised general population and hospitalised HIV population for the year 2009*

Comorbidities	General population n=5232412	HIV n=11418	p-value**
Hepatitis co-infections* , n, %	16390 (0.3%)	1397 (12.2%)	<0.0001
Hypertension, n, %	1136018 (21.7%)	927 (8.1%)	<0.0001
Diabetes mellitus, n, %	526511 (10.1%)	651 (5.7%)	<0.0001
Cardiovascular diseases¥, n, %	683316 (13.1%)	821 (7.2%)	<0.0001
Dyslipidaemia, n, %	375600 (7.2%)	425 (3.7%)	<0.0001
Obesity, n, %	282517 (5.4%)	229 (2.0%)	<0.0001
Heart failure, n, %	218697 (4.2%)	151 (1.3%)	<0.0001

**Hepatitis co-infections included hepatitis C and/or hepatitis B*
*** chi-square test*
¥ Cardiovascular diseases included coronary artery diseases, peripheral artery disease and stroke.

Table 4: *Comorbidities in all newly followed PLHIV and in those hospitalised for KD*

Comorbidities	**Total newly followed PLHIV n=1113**	**Newly followed PLHIV with KD n=66**	p-value**
Hepatitis co-infections , n, %	89 (8.0%)	4 (6.1%)	*0.5708*
Hypertension, n, %	53 (4.8%)	5 (7.6%)	*0.3701*
Mellitus diabetes, n, %	37 (3.3%)	2 (3.0%)	*1.0000*
Cardiovascular diseases¥, n, %	28 (2.5%)	5 (7.6%)	*0.0330*
Dyslipidaemia, n, %	11 (1.0%)	1 (1.5%)	*0.5007*
Obesity, n, %	14 (1.3%)	2 (3.0%)	*0.2243*
Heart failure, n, %	5 (0.4%)	1 (1.5%)	*0.2928*

**Hepatitis co-infections including hepatitis C and/or hepatitis B*
*** Fisher's exact test or chi-square test*
¥ Cardiovascular diseases included coronary artery diseases, peripheral artery disease and stroke.

Table 5: *Survival analyses*

	Cox model	Firth bias adjustment	Penalisation by data augmentation
	HR [95% CI]	HR [95% CI]	HR [95% CI]
Cardiovascular disease	3.39 [1.22-9.42]	3.77 [1.23-8.91]	3.30 [1.46-7.49]
AIDS* in women	3.67 [1.26-10.70]	3.34 [1.19-9.38]	2.45 [1.07-5.58]
AIDS* in men	0.72 [0.37-1.40]	0.71 [0.36-1.39]	0.93 [0.51-1.72]

HR: Hazard ratio ; CI: Confidence interval

Adjusted on age, obesity, co-infection, dyslipidaemia, HTA and diabetes

** AIDS = having past or present AIDS-defining illness*

Figure 1: *Cumulative incidence of KD requiring hospitalisation for all newly followed PLHIV (grey curve), for those without past or present AIDS (light bars) and for those with past or present AIDS-defining illness (dark bars).*

Figure 2: *Kaplan-Meier curve to estimate the risk of KD with time according to the AIDS status(having past or present AIDS-defining illness or not)* **A:** *for women,* **B:** *for men*

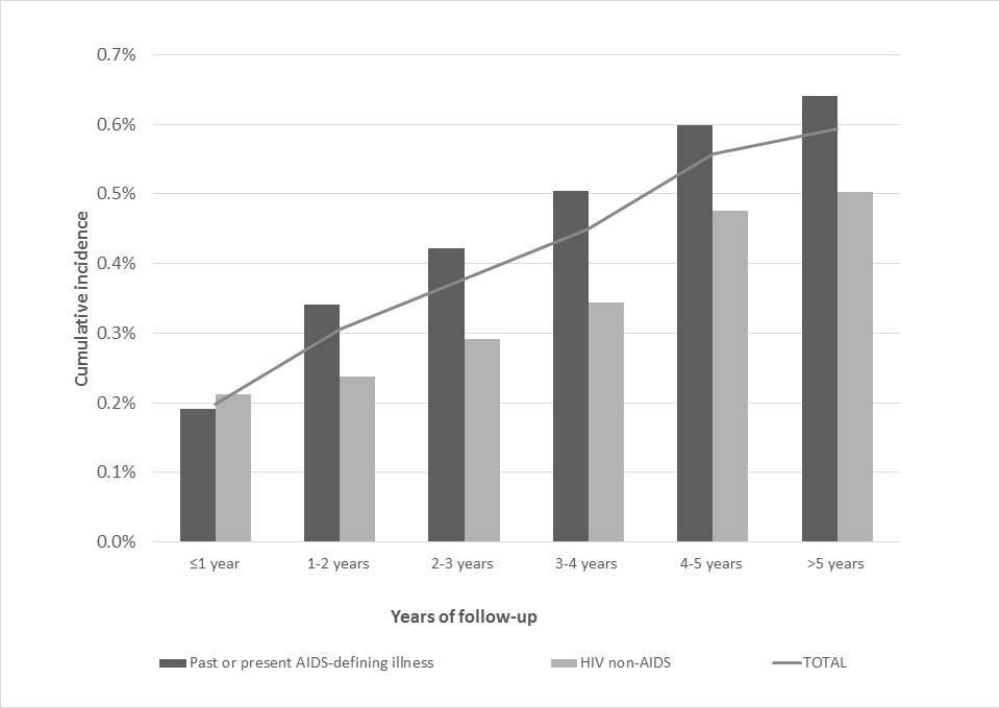

Figure 1: Cumulative incidence of KD requiring hospitalisation for all newly followed PLHIV (grey curve), for those without past or present AIDS (light bars) and for those with past or present AIDS-defining illness (dark bars).

81x60mm (300 x 300 DPI)

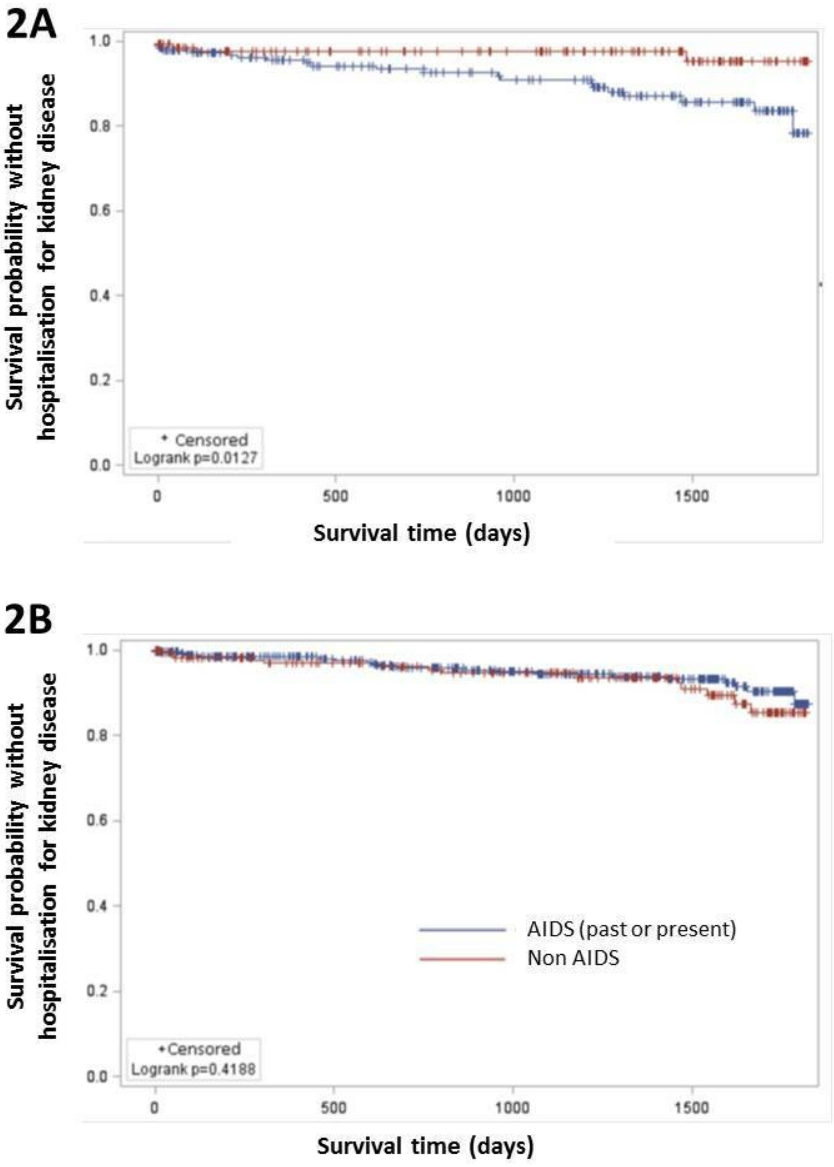

Figure 2: Kaplan-Meier curve to estimate the risk of KD with time according to the AIDS status(having past or present AIDS-defining illness or not) A: for women, B: for men

60x81mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
7Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10-tables
		(*b*) Report category boundaries when continuous variables were categorized	8-10-tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-10-tables
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.