

Risk Factors of Chronic Kidney Disease in HIV-infected Patients

Philippe Flandre,^{*†} Pascal Pugliese,[#] Lise Cuzin,[§] Corinne Isnard Bagnis,^{||} Ivan Tack,[¶] André Cabié,^{**} Isabelle Poizot-Martin,^{††} Christine Katlama,^{**} Cécile Brunet-François,^{§§} Yazdan Yazdanpanah,^{|||} and Pierre Dellamonica[‡] on behalf of the New AIDS Data group

Summary

Background and objectives The main aim of this study was determining the risk factors of chronic kidney disease (CKD) in HIV-1-infected patients.

Design, setting, participants, & measurements Patients were followed from seven large HIV reference centers in France that maintain prospective databases on HIV-1-infected patients. The main outcome was the time to CKD defined as two consecutive measures of estimated GFR ≤ 60 ml/min per 1.73 m² over ≥ 3 months. A Cox's model with delayed entry was used to search predictive factors of time to CKD.

Results From 1993 to 2006, 349 out of 7378 patients were found to have CKD. Of these, 166 had hypertension, 33 had diabetes, and 26 were antiretroviral therapy-naïve. Occurrence of acute kidney injury (hazard ratio [HR] = 2.40) and hypertension (HR = 2.39) were strongly associated with an increased risk of CKD. Patients with a durable level of CD4 count >200 cells/mm³ had a lower risk of CKD (HR = 0.63). Recent exposure to indinavir (HR = 2.03), tenofovir (HR = 1.55), and abacavir (HR = 1.37) were associated with an increased risk of CKD. Past exposure to tenofovir was also associated with an increased risk of CKD (HR = 2.23), and a trend toward significance was observed for past exposure to indinavir (HR = 1.28).

Conclusions CKD was not rare in HIV-infected patients and occurs preferentially in HIV-infected patients exposed to certain ARVs, specifically abacavir, indinavir and tenofovir. This requires closer monitoring of renal function in patients exposed to one of these drugs.

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Introduction

HIV-associated nephropathy (HIVAN), acute kidney injury (AKI), and chronic kidney disease (CKD) are important complications of HIV infection and may become increasingly important as patients live longer in the era of combined antiretroviral therapy (ART) (1). Cross-sectional studies described a 4% to 17% prevalence of reduced kidney function in diverse HIV-infected populations (2–5). A recent large European cohort study examining CKD in HIV-infected patients found a prevalence of CKD around 4% (5).

CKD and decline in renal function have been reported in association with older age, female gender, hepatitis B and C infections, diabetes, hypertension, and ART exposure (2,3,5). AKI and a decline in renal function have been reported in association with indinavir (2,6), atazanavir (7), and ritonavir (8,9). Proximal tubular dysfunction and acute tubular necrosis have been reported in patients starting tenofovir (10–13) or didanosine (14), often precipitated by drug interactions (15). The Swiss cohort has reported a reduction of the estimated GFR (eGFR) with prolonged ART exposure (16), and among ART, tenofovir

and indinavir exposures have been associated with increased risk of CKD in the EuroSIDA study (5).

Beyond the renal effect of exposure to combined ART, the importance of all factors in the development of CKD is not clearly established. An understanding of these factors, including each component of an ART regimen, HIV markers, and demographic factors related to CKD, is important to establish the relationship between ART, HIV infection, and CKD. Estimating the prevalence and risk factors for CKD in the HIV French population has rarely been documented. Because CKD stage ≥ 3 has been shown to be a very strong cardiovascular risk factor in the general population (17), better knowledge of this condition could allow better cardiovascular protection. The principal aim of this study was to determine the risk factors of developing CKD in HIV-1-infected patients.

Materials and Methods

Study Design

We performed a retrospective cohort analysis of HIV-infected patients followed from seven large HIV reference centers from seven distinct cities in France. The study design was approved by the Nadis scien-

*INSERM UMR-S 943 Pierre & Marie Curie University, Paris, France; †Laboratoire de Virologie, AP-HP, Pitié Salpêtrière, Paris, France; ‡Pôle Clinique Universitaire des Spécialités Médicales, Université Nice-Sofia Antipolis, CHU de Nice, Hôpital l'Archet, Nice, France; §Hôpital Purpan, Toulouse, France; ||AP-HP, Pitié Salpêtrière, Paris, France; ¶Hôpital Rangueil, Toulouse, France; **Centre Hospitalier Universitaire de Fort de France, Martinique, French West Indies and Centre d'Investigation Clinique, Epidémiologie Clinique, Antilles, Guyane; ††Immunologie Clinique, Hôpital Sainte-Marguerite, Marseille, France; ††AP-HP, Pitié Salpêtrière, Paris, France; §§Service des Maladies Infectieuses, CHU Nantes, France; and |||Service Universitaire de Maladies Infectieuses et du Voyageur Centre Hospitalier de Tourcoing, Tourcoing, France

Correspondence: Dr. Corinne Isnard Bagnis, Service de Néphrologie, Hôpital Pitié Salpêtrière, 47–83 boulevard de l'hôpital, AP-HP, Paris, France. Phone: 01-42-17-72-27; Fax: 01-42-17-79-14; E-mail: corinne.bagnis@psl.aphp.fr

tific committee in June 2006. Information was specifically collected for this study. These hospitals maintain prospective databases of all HIV-1-infected patients who seek care in the centers and provide written consent. The databases are implemented via an electronic medical record (18). The patients enter the cohort when they seek care in one of the centers, regardless of their HIV disease history, and all previous clinical events as well as therapeutic history are collected with appropriate dates. The electronic medical record collects demographic details, clinical events, anti-retroviral history, viral load, CD4 cell count, and routine biologic data for patients at regular 3- to 6-month intervals during routine clinical assessment. This system allows use of the databases with minimal delay, limited to automatic and manual quality controls performed before any analysis. Patients from the cohort with at least two serum creatinine measurements were included in the study.

Outcome and Measurements

The main outcome of our study was the occurrence of CKD. The glomerula filtration rate was estimated (eGFR) using the following Modification of Diet in Renal Disease (MDRD) formula: $[eGFR = 18.63 \times (\text{creatinine}/88.4)^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (for women)}]$. CKD was exclusively defined as two consecutive measures of eGFR ≤ 60 ml/min per 1.73 m² over at least 3 months, evaluated by at least two measurements. In case of CKD, the date of the first measurement of eGFR ≤ 60 ml/min per 1.73 m² was used to define the date of CKD. The definition of CKD was on the basis of clear clinical guidelines for patients with CKD stages 3 to 5, whereas there is no therapeutic consensual strategy for patients in stage 1 or 2 (19,20).

We queried appropriate databases for the following variables: gender, age, weight, height, HIV RNA levels, CD4 cell count, serum creatinine, hepatitis B and C status, hypertension status, and diabetes status. Dates of exposure to antiretroviral drugs were also available, as well as the date of occurrence of any AIDS-defining event and date of HIV diagnosis.

Data Analysis

Because of the wide period of follow-up, some antiretroviral (ARV) drugs were unavailable when the first pa-

tients experienced CKD, whereas other ARV drugs were no longer used at the end of the follow-up in 2006. We then chose a Cox’s model with delayed entry to analyze our data. The date of delayed entry was the date of the first creatinine measurement; patients cannot be diagnosed with CKD before having a creatinine measurement. Therefore, a patient having a date of first creatinine measurement at a later date than a given date of CKD was not included in the corresponding risk set (Figure 1). For instance, at time to CKD of subject A (2000), the risk set includes only subjects A, B, and C and not subjects D, E, F, and G, who enter into the model beyond 2000 (Figure 1). Because patients experiencing CKD were compared with patients followed at the same calendar period who were then able to receive the same drugs, such a model takes into account the different dates of introduction of ARV drugs. In addition, all analyses with the Cox’s model were stratified by center to consider potential differences such as therapeutic settings, laboratory measurements, and population of patients. The Cox’s model (PHREG procedure, SAS version 9.1) was then used to investigate the relationship between variables included in the model and time to CKD.

Three classes of variables were investigated. Factors known to be potentially related to CKD included fixed variables as hepatitis B status, hepatitis C status, hypertension, and diabetes. AKI was defined as a drop of 25% of eGFR compared with the mean of three preceding values with an eGFR < 90 ml/min per 1.73 m². AKI was a time-dependent variable in the model taking the value 1 after its occurrence and 0 otherwise.

Factors related to HIV infection were investigated. AIDS was also a time-dependent variable taking the value 1 after occurrence of a clinical AIDS-defining event and 0 otherwise. Instead of using CD4 cell count and HIV RNA level as simple time-dependent variables, we investigated whether the immunological and virological status during the past 2 years before CKD were associated with an increased risk of CKD. CD4 cells counts during the last 2 years before a date of CKD were used to compute the percentage of time with a CD4 count of > 200 cells/mm³. Then an indicator variable takes the value of 1 if this time

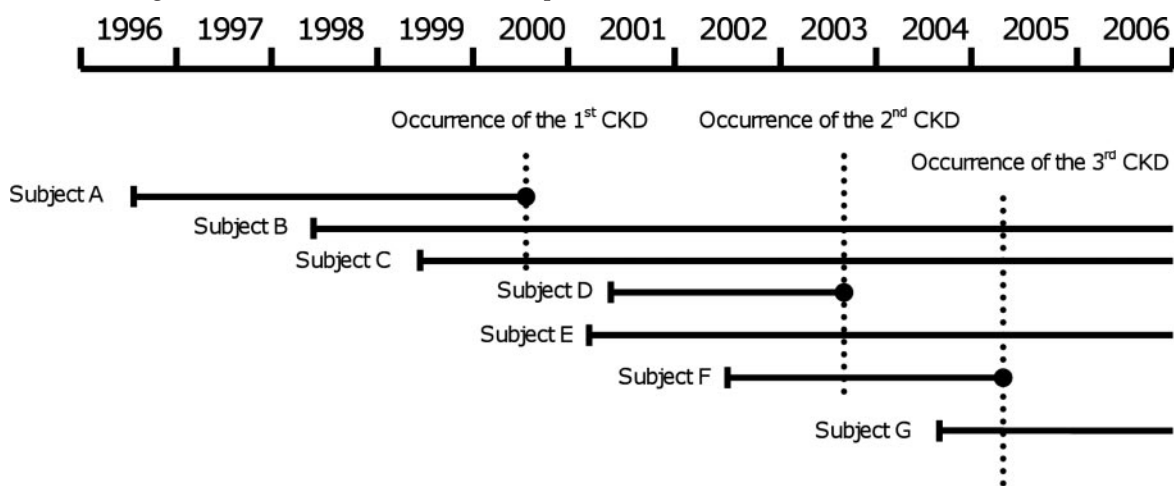


Figure 1. | The Cox’s model with delayed entry (date of first creatinine measurement): the example of seven hypothetical subjects.

was $\geq 80\%$ and 0 otherwise. A similar indicator variable was created for viral load measurements using HIV-1 RNA < 500 copies/ml as threshold.

All of the drugs used in more than 500 person-years were included in the model, although reliable findings should take into account the number of person-years associated with each drug as relative power to determine its effect. The following three drugs were not included in the model because of the number of person-years < 500 : tipranavir, darunavir, and enfuvirtide. We did not postulate that cumulative exposure to ARVs would be associated with an increased risk of CKD. Then the effect of each drug was investigated through a couple of indicator variables. We investigated whether the risk of CKD was associated with recent use (defined as current use or use within the previous 6 months) of each drug and with past use (last use > 6 months) of each drug, both variables being binary time-updated covariates.

The final model included all variables described above and was also adjusted for age, gender, body mass index (classified according to four categories: < 18.5 kg/m², ≥ 18.5 , and ≤ 25 kg/m², > 25 and ≤ 30 kg/m², and > 30 kg/m²), time since HIV diagnosis, and cumulative ARV exposure since initiation to antiretroviral therapy. Different sensitivity analyses were conducted including a modification of recent and past exposure using thresholds of 3 months and 1 month, exclusion of patients having only two creatinine measurements, and the use of 350 CD4 cells/mm³ as threshold for the immunological variable.

Results

A total of 7378 patients satisfied the inclusion criteria and were included in this analysis. The median date of the first creatinine measurement was May 2002 (interquartile range [IQR] March 2001 to July 2004). The median delay from HIV diagnosis to date of CKD or last clinic visit, whichever occurred first, was 11.2 years (IQR, 5.3 to 16.3). The median delay from HIV diagnosis to date of starting ARV, to date of the first creatinine measurement, and to date of CKD was 2.3 years (IQR, 0.2 to 6.6), 5.7 years (IQR, 0.5 to 11.4), and 8.6 years (IQR, 4.1 to 13.6), respectively. Overall 75% of patients had a first recorded creatinine measurement in the database after initiation of ART. The median eGFR at the first serum creatinine measurement was 93.8 ml/min per 1.73m² (IQR, 81.1 to 108.8) according to the MDRD formulae. The median number of serum creatinine measurements per patient and per year was 4.3 (IQR, 3.2 to 5.8) with no significant differences between patients experiencing CKD or not. The median delay between the first and last serum creatinine measurement was 4.4 years (IQR, 2.2 to 5.6).

A total of 349 (4.7%) patients experienced CKD during their follow-up. Of these, 166 (48%) had hypertension, and 33 (9.5%) had diabetes. Only 26 (7.4%) were ART-naïve. Description of the patients with and without CKD is shown in Table 1. Before time to CKD or last clinic visit, whichever occurred first, AKI had occurred in 23.8% of the patients with CKD compared with 18.2% of patients without CKD. Similarly, an AIDS-defining event occurred in

Table 1. Description of the patients without and with CKD

	MDRD					
	Patients without CKD		Patients with CKD		All Patients	
	<i>n</i> = 7029	%	<i>n</i> = 349	%	<i>n</i> = 7378	%
Male	4948	70.4	241	69.1	5189	70.3
ART-naïve ^a	770	11.0	26	7.4	786	10.7
Previous AIDS ^b	1602	22.8	102	29.2	1704	23.1
Previous acute kidney injury ^b	1277	18.2	83	23.8	1360	18.4
Hepatitis B coinfection	512	7.3	34	9.7	546	7.4
Hepatitis C coinfection	1505	21.4	77	22.1	1582	21.4
Hypertension	1018	14.5	166	47.6	1184	16.0
Diabetes	265	3.8	33	9.5	298	4.0
	Median (IQR)					
Age at HIV diagnosis (years)	31 (25.5 to 38.6) ^c		39 (30.1 to 50.1) ^d		31.2 (25.6 to 39.1)	
CD4 nadir	368 (238 to 532) ^e		288 (156 to 479)		365 (234 to 529)	
Baseline body mass index	22.3 (20.3 to 24.5) ^b		22.9 (20.7 to 25.6) ^e		22.3 (20.3 to 24.6)	
Delay from HIV diagnosis to initiation of ART (years)	2.3 (0.2 to 6.6) ^c		2 (0.25.7) ^d		2.2 (0.2 to 6.6)	

MDRD, Modification of Diet in Renal Disease; IQR, interquartile range; CKD, chronic kidney disease; ART, antiretroviral therapy.

^aAt time of CKD or last clinic visit, whichever occurred first.

^bInformation missing in 32 patients.

^cInformation missing in 48 patients.

^eInformation missing in four patients.

^dInformation missing in two patients.

^eInformation missing for one patient.

Table 2. Number of patients exposed to each drug since their first eGFR

Calendar years	AZT	3TC	ABC	DDI	DDC	D4T	TDF	FTC	NVP	EFV	FAPV	SQV	IDV	NFV	LPV	ATV
≤1994	101	0	0	34	18	4	0	0	0	0	0	2	0	0	0	0
1995 to 1996	455	292	0	207	268	184	0	0	1	1	0	93	153	1	0	0
1997 to 1998	621	686	34	349	225	559	0	0	150	49	1	246	378	228	1	0
1999 to 2000	762	1056	292	522	105	798	1	3	402	359	32	218	374	379	74	2
2001 to 2002	2050	2936	1211	1218	116	1273	474	29	896	844	159	327	532	462	694	10
2003 to 2004	2731	4081	1676	1230	89	900	1390	179	1114	1021	439	364	488	409	1347	530
2005 to 2006	2768	4481	2128	1030	36	435	2126	1366	1105	1057	878	358	233	240	1453	1314
Overall	4199	5598	2774	2192	461	1920	2508	1375	1865	1790	1135	845	1141	883	2041	1373

3TC, —; ABC, —; DDI, —; DDC, —; D4T, —; TDF, —; FTC, —; NVP, —; EFV, —; FAPV, —; SQV, —; IDV, indinavir; NFV, —; LPV, —; ATV, eGFR, estimated GFR; AZT, azidothymidine.

102 (29.2%) and 1602 (22.8%) patients with and without CKD, respectively. The 6592 ART-experienced patients had a median time exposure of 8.2 years (IQR, 4.1 to 10.5) for a median number of seven drugs received (IQR, 4 to 9). The number of patients exposed to each drug since their entry into the Cox’s model (their first GFR estimation) is given in Table 2. For instance, 2768 patients received an azidothymidine (AZT)-containing regimen in the years 2005 to 2006, whereas overall, 4199 (56.9%) out of 7378 patients received at least one time an AZT-containing regimen. The rate of CKD varied markedly across the different calendar periods from 3.9/1000 person-years to 16.1/100 person-years (Table 3). The median number of CD4 count measurements per patient and per year was 4.3 (IQR, 3.2 to 5.5) over a median time of 7.3 years (IQR, 3.6 to 10.3). The median number of HIV RNA measurements per patient and per year was four (IQR, 3.2 to 4.9) over a median time of 6.8 years (IQR, 3.6 to 9.6).

The results of the Cox’s proportional hazards model are shown in Table 4. In the unadjusted analysis, neither hepatitis B or C status nor the time spent with HIV-1 RNA <500 copies/ml were significantly associated with an increased risk of CKD. Several drugs including lamivudine, stavudine, tenofovir, indinavir, lopinavir, and atazanavir as past or as recent exposure were associated with an increased hazard ratio (HR) of CKD, whereas recent exposure to zidovudine, didanosine, and zalcitabine were associated with a reduced risk of CKD.

In the multivariate model, occurrence of AKI (HR = 2.40, $P < 0.0001$) and arterial hypertension (HR = 2.39, $P < 0.0001$) were strongly associated with an increased risk of CKD. Patients with a durable level of CD4 count of >200 cells/mm³ had a lower risk of CKD (HR = 0.63, $P = 0.0003$), whereas HIV-RNA <500 copies/ml did not significantly lower the risk of CKD (HR = 0.88, $P = 0.27$). Recent exposure to indinavir (HR = 2.03, $P < 0.0001$), to tenofovir (HR = 1.55, $P = 0.02$), and to abacavir (HR = 1.37, $P = 0.03$) remained independently associated with an increased risk of CKD, whereas a trend toward significance was observed for atazanavir (HR = 1.47, $P = 0.09$). Past exposure to tenofovir was also associated with an increased risk of CKD (HR = 2.23, $P = 0.001$), and a trend toward significance was observed for past exposure to indinavir (HR = 1.28, $P = 0.08$). Additional sensitivity analyses resulted in consistent findings, even after considering a period of 3 months or 1 month to define recent and past exposure or after exclusion of patients having only two measures of serum creatinine (data not shown). The use of 350 cells/mm³ as threshold for the immunological variable leads to a HR = 0.73 (95% CI, 0.57 to 0.93, $P = 0.01$), and similar HRs were found for the other variables.

Twenty-five patients with CKD had past exposure to tenofovir (last use >6 months), 16 of whom had a first creatinine measurement before initiation of tenofovir. For these patients, the median GFR at the last estimation before initiation of tenofovir was 76.7 ml/min per 1.73 m² (IQR,

Table 3. Rate of CKD across the different calendar periods

Years	Number of patients			Person-years since First eGFR	Number with CKD	Rate/1,000 Person-years (95% CI)
	HIV Diagnosis	Initiation of ART	First GFR Estimation			
≤1994	3532	1062	254	510.8	2	3.9 (0 to 9.3)
1995 to 1996	710	1260	450	870.2	14	16.1 (7.7 to 24.5)
1997 to 1998	624	1312	365	1787.7	27	15.1 (9.4 to 20.8)
1999 to 2000	589	793	583	2610.4	11	4.2 (1.7 to 6.7)
2001 to 2002	638	745	2728	5849.1	64	10.9 (8.3 to 13.6)
2003 to 2004	716	77	1614	10086.6	122	12.1 (9.9 to 14.2)
2005 to 2006	543	643	1384	10605.1	109	10.3 (8.3 to 12.2)

CI, confidence interval.

Table 4. Results of the Cox's model

Variable	Unadjusted		Adjusted ^a	
	HR (95% CI)	P	HR (95% CI)	P
Occurrence of acute kidney injury	2.73 (2.09 to 3.58)	<0.01	2.40 (1.80 to 3.20)	<0.01
Time with CD4 >200 cells/mm ^{3a}	0.48 (0.38 to 0.61)	<0.01	0.63 (0.48 to 0.81)	0.03
Time with VL <500 copies/ml ^a	1.02 (0.82 to 1.27)	0.85	0.88 (0.69 to 1.11)	0.27
Occurrence of an AIDS-defining event	1.73 (1.369 to 2.19)	<0.01	1.19 (0.93 to 1.54)	0.17
Hepatitis B	1.34 (0.94 to 1.91)	0.11	1.13 (0.78 to 1.63)	0.53
Hepatitis C	0.90 (0.69 to 1.17)	0.42	1.07 (0.81 to 1.41)	0.65
Hypertension	4.36 (3.52 to 5.39)	<0.01	2.39 (1.88 to 3.04)	<0.01
Diabetes	2.52 (1.75 to 3.62)	<0.01	1.23 (0.84 to 1.80)	0.30
Past exposure				
AZT	1.12 (0.85 to 1.47)	0.43	0.88 (0.62 to 1.26)	0.48
3TC	1.67 (1.14 to 2.45)	0.09	0.89 (0.52 to 1.51)	0.89
ABC	1.25 (0.88 to 1.77)	0.22	0.92 (0.62 to 1.36)	0.67
DDI	1.09 (0.86 to 1.39)	0.48	0.84 (0.63 to 1.23)	0.25
DDC	1.01 (0.77 to 1.32)	0.95	0.93 (0.69 to 1.26)	0.64
D4T	1.15 (0.90 to 1.48)	0.27	0.93 (0.67 to 1.29)	0.67
TDF	2.61 (1.69 to 4.04)	<0.01	2.23 (1.37 to 3.63)	0.01
FTC	1.41 (0.20 to 10.13)	0.73	1.03 (0.14 to 7.66)	0.98
SQV	0.98 (0.70 to 1.37)	0.88	0.74 (0.51 to 1.08)	0.12
IDV	1.38 (1.08 to 1.77)	0.01	1.28 (0.97 to 1.70)	0.08
NFV	0.85 (0.63 to 1.15)	0.30	0.78 (0.56 to 1.09)	0.15
LPV	1.40 (0.92 to 2.12)	0.11	1.04 (0.66 to 1.64)	0.88
ATV	2.06 (0.75 to 5.63)	0.16	1.24 (0.43 to 3.55)	0.69
FAPV	1.38 (0.75 to 2.55)	0.30	0.93 (0.47 to 1.84)	0.83
NVP	0.83 (0.60 to 1.16)	0.27	0.75 (0.52 to 1.09)	0.13
EFV	1.13 (0.83 to 1.53)	0.44	1.00 (0.72 to 1.40)	0.99
Recent exposure				
AZT	0.78 (0.59 to 1.04)	0.10	0.62 (0.42 to 0.91)	0.02
3TC	1.77(1.27 to 2.45)	0.01	1.24 (0.76 to 2.04)	0.39
ABC	1.40 (1.08 to 1.81)	0.12	1.37 (1.03 to 1.82)	0.03
DDI	0.77 (0.55 to 1.07)	0.12	0.75 (0.52 to 1.08)	0.13
DDC	0.33 (0.12 to 0.91)	0.03	0.40 (0.14 to 1.14)	0.09
D4T	1.56 (1.15 to 2.11)	0.04	1.17 (0.81 to 1.70)	0.4
TDF	1.67 (1.24 to 2.31)	0.01	1.55 (1.09 to 2.20)	0.02
FTC	1.06 (0.56 to 2.00)	0.85	0.94 (0.47 to 1.89)	0.87
SQV	1.04 (0.66 to 1.63)	0.88	0.94 (0.59 to 1.51)	0.8
IDV	2.32 (1.68 to 3.21)	<0.01	2.03 (1.42 to 2.90)	<0.01
NFV	0.94 (0.58 to 1.53)	0.80	0.96 (0.58 to 1.59)	0.87
LPV	1.36 (0.99 to 1.85)	0.05	1.30 (0.92 to 1.85)	0.14
ATV	1.77 (1.18 to 2.65)	0.06	1.47 (0.94 to 2.30)	0.09
FAPV	0.75 (0.42 to 1.35)	0.34	0.72 (0.39 to 1.32)	0.29
NVP	0.96 (0.69 to 1.33)	0.80	1.08 (0.76 to 1.54)	0.68
EFV	0.97 (0.70 to 1.35)	0.85	1.02 (0.71 to 1.46)	0.92

^aValues after adjustment for age, gender, BMI, time since HIV diagnosis, cumulative exposure to any ART, and number of ART drugs received. 3TC, lamivudine; ABC, abacavir; DDI, didanosine; DDC, zalcitabine; D4T, stavudine; TDF, tenofovir; FTC, emtricitabine; NVP, névirapine; EFV, efavirenz; FAPV, fosAmprenavir; SQV, saquinavir; IDV, indinavir; NFV, nelfinavir; LPV, lopinavir; ATV, atazanavir. Bold values indicated statistically significant difference.

69 to 85) (whereas it was of 93.8 ml/min per 1.73 m² in the whole group), and the last estimation under tenofovir-containing regimen was 56.7 ml/min per 1.73 m² (IQR, 52.2 to 63.3). This corresponds to a median decrease of 16.5 ml/min per 1.73 m² (IQR, -32.5 to -4.6) over a median period of 3.8 years (IQR, 2 to 4.2) on the basis of a median of 4.5 creatinine measurements (IQR, 4 to 8).

We studied eGFR evolution in the more recently HIV-diagnosed patients (after 2003) being either ART-naïve or still under their first ART regimen. Overall 755 patients were selected, 458 (61%) of whom were ART-naïve. The median difference between the first and last eGFRs was

-0.51 ml/min per 1.73 m² (IQR, -11 to 9.3) on the basis of a median of seven (IQR, 4 to 11) creatinine measurements over a median period of 17 months (IQR, 7.5 to 27.3). There was no significant difference between ART-naïve and ART-experienced patients (median decrease of -0.50 *versus* -0.53 ml/min per 1.73 m²). The ART-experienced patients received zidovudine (*n* = 148), lamivudine (*n* = 216), abacavir (*n* = 56), tenofovir (*n* = 91), emtricitabine (*n* = 78), efavirenz (*n* = 51), lopinavir (*n* = 127), fosamprenavir (*n* = 35), or atazanavir (*n* = 31). The other ARTs were received in less than 10% of ART-experienced patients. Patients receiving a tenofovir-containing regimen had a signifi-

cantly greater eGFR decrease compared with patients who received any other ART-containing regimen (median decrease of -5.9 versus 0.7 ml/min per 1.73 m², $P = 0.004$). A similar difference was observed for patients receiving an emtricitabine-containing regimen, although among the 78 patients receiving emtricitabine 75 (96%), patients also received tenofovir.

Discussion

Many studies have investigated predictive factors of GFR changes (21–23), whereas fewer studies have been conducted on large data sets investigating factors associated with CKD (5,24,25). To our knowledge, our study is the largest cohort of HIV-infected adults investigating risk factors of CKD, especially the effect of each ARV drug. Hypertension, previous AKI, and CD4 cell counts were all found to be independently related to CKD. We also found some evidence that patients treated with tenofovir and indinavir, and to a lesser extent abacavir, had a higher risk for CKD. Our study shows statistical association between ARV drugs and CKD that needs to be documented further to identify nephrotoxic mechanisms. Tenofovir and indinavir have been shown to be related to nephrotoxicity in many studies (2,5,6,10,11,25). Some factors (hepatitis B or C and diabetes) traditionally reported as related to CKD in persons with or without HIV-1 infection were not found to be independently associated with the occurrence of CKD in our analysis (5,26,27).

Most previous studies of the relationship between renal function and antiretrovirals have been on the basis of small or moderate patient groups and have tended to focus exclusively on tenofovir (16,21,22,25,27,28). In EuroSIDA, 4474 patients were analyzed, and many antiretrovirals were investigated as being associated with chronic renal failure. CKD, however, was determined only at a baseline point, and no distinction was made between recent or past exposure to antiretrovirals (5). They found an identical prevalence as in our study, and any tenofovir (TDF) use, as well as any indinavir (IDV) use, was associated with a higher risk of CKD (5). A recent study investigated the effect of tenofovir on renal function in 1647 ARV-naïve HIV-infected patients (25). Again, this study focused on tenofovir exposure and concluded that tenofovir was associated with greater effect on decline in renal function. We also found that recent or current use of tenofovir increased the risk of CKD but also that past use was independently associated with an increased risk of CKD. Interestingly, we found that current or recent use of abacavir was associated with CKD. Abacavir has been associated with a higher risk of cardiovascular events (CVE) (29), and a recent study showed a significant independent association between decreased kidney function and increased risk of CVE in HIV-infected patients (30). Further studies are needed to confirm whether abacavir is associated with CKD and whether it is associated with CVE through the kidney function. Regarding ART exposition, recent use of AZT seems to be related to an apparent lower risk of CKD (HR = 0.62). This effect of AZT should be interpreted as the nonuse of a detrimental Nucleoside Reverse Transcriptase inhibitor (abacavir or tenofovir) rather than a true beneficial effect on AZT on renal function.

Renal toxicity of TDF could not be shown in clinical trials, even with long term follow-up (22,31), although patients receiving tenofovir had a greater GFR decline over time (22). This may be due to three major differences between cohorts and randomized trials. The first is the population size, which is critical when the prevalence of such a complication is low (4%). We provide here data on more than 7000 patients with a median number of serum creatinine measurements of four per year during a median follow-up of 4 years. Second, patients in cohort studies are not selected conversely to clinical studies regarding risk factors. Thus, cohorts provide results that are useful in clinical practice, as compared with clinical trials, providing results that can only be applied to a comparable selected population. Third, even “long-term” clinical trials usually do not exceed 3 years of follow-up, and the cumulative role of TDF may not be apparent on this duration. In our data, the median delay between the initiation of ART and occurrence of CKD was 5.4 years.

In the adjusted model, we found that hypertension but not diabetes was associated with CKD. Mocroft *et al.* (5) suggested that most patients with diabetes also had hypertension. Only 21 (6%) of the 349 patients with CKD had both risk factors. The association of CD4 cell count and CKD or GFR decline has been found in several studies (23,26,32,33). Interestingly, we found an association between the time spent with a CD4 count of >200 cells/mm³ during the last 2 years and a lower risk of CKD. A recent study (23) found a relationship between suppression of HIV-1 replication and improvement of renal function, whereas others (33) found that higher baseline HIV-1 RNA and increases in HIV RNA were strongly associated with declining kidney function. In both unadjusted and adjusted analysis, we did not find such an association. Although expected, we showed that occurrence of AKI was strongly associated with a higher risk of CKD.

Analysis of observational data is a difficult task, and the choice of the model is a key feature for an appropriate interpretation of the results. Figure 1 illustrates that a Cox's model with delayed entry was appropriate to handle the different dates of introduction of ARV drugs. A simple Cox's model, even adjusted for calendar periods, would not take into account such a difficulty. Table 2 confirmed the wide distinct period of antiretroviral use in our cohort of patients. Because renal disease became important in the context of the HIV infection, GFR estimation is now routinely available in particular before initiation of any antiretroviral therapy. Such a baseline value of GFR was not included in our analysis because it was available only for 25% of our patients but should be taken into account in further studies. The different populations of patients and any potential therapeutic practice between the different centers have been taken into account via a stratified analysis.

Our study has some limitations. First, we did not use a gold standard measurement of GFR for practical reasons. The eGFR is widely considered to be a direct measure of kidney function and reduces before the onset of symptoms of kidney failure (34,35). We chose to use MDRD evaluation of GFR because it has been previously shown to have a level of precision and accuracy sufficient for clinical decision making (36,37). All methods of GFR estimation

have been discussed and compared in some studies with gold standard methods of creatinine clearance measurements. In the United States HIV cohort, some discrepancies have been shown between Cockcroft-Gault and MDRD, but no gold standard was applied to the population (38). In a recent Italian study, Cockcroft-Gault and MDRD estimates (*versus* gold standard) showed a satisfactory correlation (36). Plasmatic and urinary cystatin C can be measured routinely and provide good information on serum creatinine clearance using the CKD-EPI estimation, as well as on tubular dysfunction using the serum/urinary ratio (39). Large cohort studies using this estimation of eGFR are ongoing.

Because the French patients' rights do not allow capture of ethnicity in our database, we are not able to provide data on this item, known as relevant regarding CKD in HIV-infected patients. Thus, HIVAN, known to be more frequent in black patients, is also more frequent in the absence of virologic control (33). Because most of the patients developing CKD in our cohort were receiving effective antiviral therapy, we do not feel that HIVAN could be a major confounding factor in our results. This limitation could bias the prevalence of CKD in patients from the Caribbean island center, but it is minimized by the stratified analysis as mentioned above. As in any observational study, we may have failed to capture unknown confounding patient characteristics. As an example, we do not have exhaustive data on the use of other potential nephrotoxic drugs. Bias may be introduced by the differences in the frequency of laboratory measurements depending on the presence or absence of CKD, but in our study, this was not different between patients with CKD and those without. Finally, we did not collect information regarding genetic factors that have been shown to be related to kidney dysfunction in TDF-receiving patients (40).

In summary, in 7378 well-documented patients, CKD was diagnosed in 4.7%. On the basis of our results, closed monitoring of renal function seems warranted in HIV-infected patients with risk factors such as hypertension, previous AKI, and low CD4 cell counts and in those treated with abacavir, indinavir, or tenofovir. More precise measurements of renal function are needed, because severe tubular dysfunction without serum creatinine clearance diminution has also been described and may affect long term renal safety of HIV-infected patients (41,42).

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The New Aids Data Group: P. Enel, V. Obry-Roguet, M.P. Drogoul-Vey, A. Ménard, S. Bréigigon, O. Faucher, F. Brun, J.L. Mattéi, M. Orticoni, M.J. Soavi, H. Bertone, S. Benhaim, M.J. Du-

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