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Original article

Prevalence and risk factors of mild chronic renal failure in HIV-infected patients: influence of female gender and antiretroviral therapy

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ABSTRACT

Background: In people living with HIV, much is known about chronic kidney disease, defined as a glomerular filtration rate under 60 mL/min. However, there is scarce data about prevalence and risk factors for milder impairment (60–89 mL/min).
Objective: The present study aims to assess the influence of sex, antiretroviral therapy, and classical risk factors on the occurrence of mild decreased renal function in a large Spanish cohort of HIV-infected patients.
Methods: Cross-sectional, single center study, including all adult HIV-1-infected patients under antiretroviral treatment with at least two serum creatinine measures during 2014, describing the occurrence of and the risk factors for mildly decreased renal function (eGFR by CKD-EPI creatinine equation of 60–89 mL/min).
Results: Among the 4337 patients included, the prevalence rate of mildly reduced renal function was 25%. Independent risk factors for this outcome were age older than 50 years (OR 3.03, 95% CI 2.58–3.55), female sex (OR 1.23, 95% CI 1.02–1.48), baseline hypertension (OR 1.57, 95% CI 1.25–1.97) or dyslipidemia (OR 1.48, 95% CI 1.17–1.87), virologic suppression (OR 1.88, 95% CI 1.39–2.53), and exposure to tenofovir disoproxil-fumarate (OR 1.67, 95% CI 1.33–2.08) or ritonavir-boosted protease-inhibitors (OR 1.19, 95% CI 1.03–1.39).

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Conclusions: Females and patients over 50 seem to be more vulnerable to renal impairment. Potentially modifiable risk factors and exposure to tenofovir disoproxil-fumarate or ritonavir-boosted protease-inhibitors are present even in earlier stages of chronic kidney dysfunction. It remains to be determined whether early interventions including antiretroviral therapy changes (tenofovir alafenamide, cobicistat) or improving comorbidities management will improve the course of chronic kidney disease.

Introduction

In most countries with broad access to antiretroviral therapy, chronic kidney disease (CKD) in people living with HIV infection is now more likely to be the result of non-HIV associated conditions,[1,2] and it might have a higher prevalence and earlier onset than in age-matched uninfected individuals.[3–5] Although there is a low overall risk of developing end-stage renal disease,[6,7] decreasing GFR is related to a significantly increased risk of cardiovascular events and mortality.[8,9]

Even patients with milder grades of renal dysfunction already have sizable medical costs that can be attributed to renal function impairment.[10] Moreover, a considerable number of the antiretroviral drugs and antibiotics undergo renal elimination and demand dose-adjustments according to kidney function.[11] Lastly, the increasing exposure to some antiretroviral drugs can lead to progression to kidney disease, even in individuals with initially normal renal function.[12] Therefore, in clinical practice, it is important for the attending physician to identify the presence of incremental baseline risk factors and intervene where they are potentially modifiable and as early as possible.

Several studies have already been published evaluating the presence of risk factors for CKD stage ≥ 3.[7,13–18] However, there is a lack of information regarding the factors associated with earlier stages of renal dysfunction, also associated with increased risk of complications,[9,19] but in which preventive actions would be more feasible.

The aim of the present study is therefore to assess the influence of sex, type of antiretroviral therapy (ART), and the classical risk factors on mildly decreased renal function (CKD EPI eGFR 60–89 mL/min/1.73 m^2) among an urban population of stable patients with HIV-infection in a large Spanish cohort.

Methods

Study design

This was an observational, cross-sectional, single center study. The study project was reviewed and approved by the Institutional Review Board (CEIC Hospital Clinic i Provincial, Barcelona, Spain, IRB# 2014/1080). Eligible patients were all adult HIV-1-infected patients (>18 years old) with at least two serum creatinine measures during the calendar year of 2014. A description of the prevalence of the various stages of CKD of the entire cohort was published elsewhere.[20] For the current analysis, patients were excluded if they presented an estimated GFR above 181 mL/min/1.73 m^2, a diagnosis of chronic kidney disease (eGFR < 60 mL/min per 1.73 m^2), dialysis and/or kidney transplantation, or if they were recipients of a hepatic allograft.

The main objectives of our study were to describe the occurrence of mildly decreased renal function, defined as two consecutive measures of eGFR between 60 and 89 mL/min/1.73 m^2 over at least three months, and to determine the variables associated with a higher risk of this event. eGFR was obtained using the CKD-EPI creatinine equation.[21] As in other publications, we considered the African-American coefficient factor as not applicable to black patients from Africa, Europe and Antilles.[22,23]

The following demographic, clinical and laboratory parameters were abstracted from the HIV clinical database: age, sex, race, body mass index, hypertension (use of anti-hypertensive medication at CKD diagnosis), diabetes mellitus (glucose intolerance requiring pharmacological intervention), hyperlipidemia (use of hypolipidemic medication at CKD diagnosis), prior cardiovascular event, viruses, time of HIV-infection diagnosis, mode of transmission, AIDS stage, CD4 and viral load (current and nadir), current and previous antiretroviral treatment, hepatitis B coinfection (positive serology) and hepatitis C coinfection (positive serology + detectable HCV-RNA). Urinalysis for proteinuria was not available for the present study.

Data analysis

Demographic, clinical and laboratory parameters were described for patients with and without mildly decreased renal function. Quantitative variables were expressed as median and interquartile range. Analysis of normality of quantitative variables was performed using the Kolmogorov–Smirnov test, and because none of them displayed a normal distribution, nonparametric tests were used to compare these variables. Categorical variables were expressed as number, percentage, and 95% CI; the Chi-square test was used for comparisons. For all tests, statistical significance is considered if the p-value < 0.05. To identify risk factors associated with mildly decreased renal function, we performed a stepwise binary logistic regression analysis. Variables included in the model were those with a p-value < 0.05 in univariate analysis, or those considered relevant by other published studies. Statistical analyses were performed using the Predictive Analytics Software Statistics for Windows, v21.0 (SPSS Inc, Chicago, IL).

Results

The eligible population consisted of 4493 patients. After excluding 116 subjects with chronic kidney disease, 11 patients in dialysis, eight recipients of kidney transplantation, and 21 recipients of hepatic transplantation, 4337 individuals were included for analysis (Fig. 1).

The overall median age was 44 years-old (range 18–85), 47 (18–85) for females and 44 (18–83) for males.

The overall prevalence rate of mildly reduced renal function (eGFR 60–89 mL/min per 1.73 m^2) was 25.0% (1083 patients). The median eGFR among patients with normal renal function was 103.5 (IQR 97.3–110.3) mL/min/1.73 m^2; the median eGFR among patients with mildly reduced renal function was 79.7 (IQR 73.0–85.1) mL/min/1.73 m^2.

Univariate analysis

Compared with patients with normal renal function, patients with mildly reduced eGFR were older, had a higher percentage of females, higher body mass index, higher proportion of heterosexuality, more prior AIDS events, and more comorbidities like hypertension, dyslipidemia, diabetes, and prior cardiovascular disease. They were also prone to longer durations of HIV-infection, higher initial and peak viral loads, lower nadir of CD4+ cell count, higher frequency of prior AIDS events, but a higher proportion of patients presented viral suppression on treatment (Table 1). The overall length of exposure to any regimen, as well as the total exposure to protease inhibitors (boosted or not), tenofovir disoproxil-fumarate, and PI plus tenofovir disoproxil-fumarate were higher among individuals with mildly reduced eGFR (Table 2).

Sex disparities

The median eGFR was 94.9 (IQR 81.3–105) mL/min/1.73 m^2 for females and 96.6 (IQR 84.2–106.3) mL/min/1.73 m^2 for males ($p = 0.005$). Females had a significantly higher proportion of mildly impaired renal function compared to males (29.2% vs. 23.9%, $p = 0.002$, Table 3).

Compared to men, women were older, had higher proportion of black race, higher prevalence of HCV-coinfection, longer duration of HIV-infection, higher proportion of heterosexual route of acquisition, of drug injecting drugs and prior AIDS events, a lower nadir of CD4+ cell count, a more frequent exposure to PI or boosted-PI with tenofovir disoproxil-fumarate, and a higher proportion of current therapy with PI, but a lower proportion of current ART with tenofovir disoproxil-fumarate.

Multivariate analysis

After multivariate adjustment for demographics, traditional risk factors for kidney disease, and HIV-related characteristics,

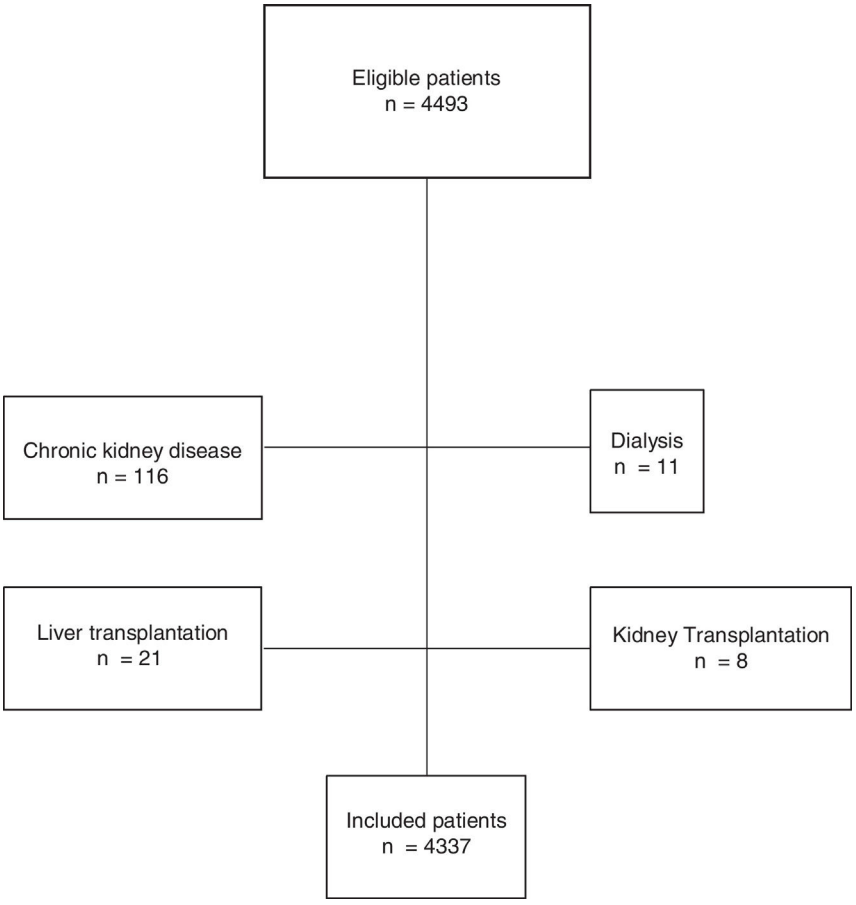

Fig. 1 – Flow diagram of the studied population.

Table 1 – Demographic and HIV-related characteristics of the global cohort and comparative analysis regarding the presence of mildly-reduced eGFR (glomerular filtration rate, estimated by CKD-EPI creatinine equation, between 60 and 89 mL/min/1.73 m^2).

Variable	Global cohort	Normal eGFR	Mildly-reduced eGFR	*p*-value
Number of patients	4337	3254	1083	–
Age, years[a]	44 (14)	43 (14)	50 (13)	**<0.001**
Female gender, n (%)	819 (18.9)	580 (17.8)	239 (22.1)	**0.002**
Black race, n (%) (n = 2729)	55 (2.0)	40 (1.8)	15 (2.5)	0.281
Body mass index, kg/m^2[a] *(n = 1373)*	22.9 (3.5)	22.8 (3.4)	23.2 (3.3)	**0.040**
Hypertension, n (%)	530 (12.2)	296 (9.1)	234 (21.6)	**<0.001**
Diabetes mellitus, n (%)	199 (4.6)	120 (3.7)	79 (7.3)	**<0.001**
Dyslipidemia, n (%)	528 (12.2)	302 (9.3)	226 (20.9)	**<0.001**
Cardiovascular events, n (%)	168 (3.9)	97 (3.0)	71 (6.6)	**<0.001**
HBV coinfection, n (%)	145 (3.3)	100 (3.1)	45 (4.2)	0.325
HCV coinfection, n (%) (n = 4329)	951 (22.0)	708 (21.8)	243 (22.5)	0.639
Duration of HIV infection, years[a] *(n = 4313)*	10.7 (13.9)	9.6 (13.7)	14.1 (12.6)	**<0.001**
Route of HIV acquisition, n (%)				
Heterosexual	1116 (25.7)	788 (24.2)	328 (30.3)	**<0.001**
Homosexual	2590 (59.7)	1997 (61.4)	593 (54.8)	**<0.001**
Injecting-drug abuse	602 (13.9)	445 (13.7)	157 (14.5)	0.681
Another route	48 (1.1)	37 (1.1)	11 (1.0)	0.778
Unknown	228 (5.3)	175 (5.4)	53 (4.9)	0.536
Prior AIDS events, n (%)	837 (19.3)	578 (17.8)	259 (23.9)	**<0.001**
HIV suppression, n (%)				
On treatment	3840 (88.5)	2825 (86.8)	1015 (93.7)	
Without treatment	29 (0.7)	23 (0.7)	6 (0.6)	**<0.001**
No suppression	468 (10.8)	406 (12.5)	62 (5.7)	
Viral load, copies/mL[a]				
First	23,622 (116,567)	22,300 (105,867)	28,670 (160,438)	**0.018**
Higher	67,951 (233,350)	62,934 (209,910)	88,730 (286,825)	**<0.001**
CD4 cell count, cells/mm^3				
Lower (nadir)	252 (237)	264 (237)	219 (240)	**<0.001**
Current	633 (375)	634 (372)	626 (394)	0.991

[a] Results expressed as median and interquartile range (IQR).
HCV, hepatitis C virus; HBV, hepatitis B virus. Significant $p < 0.05$.

female sex was associated with a 23% increased risk for renal dysfunction (Table 4). Individuals older than 50 years had a three-fold higher risk for mildly reduced eGFR compared to the under 50s. Hypertension and dyslipidemia were also independently associated with this outcome. Subjects under virological suppression had an almost 2.0-fold greater risk of renal impairment. Previous tenofovir disoproxil-fumarate and protease-inhibitor exposure were also significant risk factors for mild impaired renal function.

Analyses were also stratified by sex to evaluate possible effect modification: among men, older age (OR 2.57; 95% CI 2.17–3.04), dyslipidemia (OR 1.56; 95% CI 2.17–3.04), viral suppression (OR 2.05; 95% CI 1.47–2.84), each additional year of exposure to tenofovir disoproxil-fumarate (OR 1.08; 95% CI 1.05–1.11), and coinfection with hepatitis B (OR 1.48; 95% CI 1.01–2.17) remained independently associated with increased risk for mild renal impairment, whereas coinfection with hepatitis C (OR 0.74; 95% CI 0.57–0.95) was related to a lower risk for this event. On the other hand, among women, older age (OR 2.84; 95% CI 2.07–3.89), hypertension (OR 1.62; 95% CI 1.05–2.50), viral suppression (OR 2.19; 95% CI 1.20–4.03), and each additional year of exposure to protease inhibitors (OR 1.05; 95% CI 1.01–1.08) remained as independent variables associated with renal dysfunction.

Discussion

The main findings of this study, which involved a large sample of patients with well-controlled HIV-infection, were: (a) one quarter of the patients had mildly decreased renal function; (b) women appear to be more susceptible to changes in renal function than men; and (c) traditional and non-traditional risk factors were associated with this outcome.

Renal involvement among patients with HIV-infection is highly variable, but there is a higher risk of developing end-stage renal disease (ESRD) in comparison with the non-infected population. A recent report from the North American AIDS Cohort Collaboration on Research and Design (NAACCORD) in USA and Canada, including 38,354 HIV-infected adults from 2000 to 2009, showed a three-fold higher incidence of ESRD than in the general population. Patients with HIV-infection and ESRD were more likely to be of black race, have diabetes mellitus or hypertension, inject drugs, or have a prior AIDS-defining illness.[24] In the same way, in Europe, a German cohort study of 9198 patients observed that the incidence of ESRD was more than two times that of the general population. Risk factors for ESRD were black ethnicity, use of injecting drugs, and HCV-coinfection. Interestingly, the prevalence of ESRD increased over time, especially among

Table 2 – Antiretroviral treatment used by patients with normal eGFR and with mildly-reduced eGFR.

Variable	Global cohort	Normal eGFR	Mildly-reduced eGFR	*p*-value
Number of patients	4337	3254	1083	
Currently on ART, n (%)	4199 (96.8)	3132 (96.3)	1067 (98.5)	**<0.001**
Time under current ART regimen, years[a]	1.3 (3.6)	1.2 (3.5)	1.5 (3.9)	**<0.001**
Current ART regimen, n (%)				
No treatment	138 (3.2)	112 (3.7)	16 (1.5)	
NNRTI-based	2336 (53.9)	1759 (54.1)	577 (53.3)	**0.005**
PI-based	136 (3.1)	102 (3.1)	34 (3.1)	
Boosted PI-based	1257 (29.0)	930 (28.6)	327 (30.2)	
Integrase Inh-based	439 (10.1)	316 (9.7)	123 (11.4)	
Other	31 (0.7)	25 (0.8)	6 (0.6)	
Patients currently using, n (%)				
Tenofovir	2825 (65.1)	2169 (66.7)	656 (60.6)	**<0.001**
Indinavir	0	0	0	–
Atazanavir	308 (7.1)	237 (7.3)	71 (6.6)	0.419
Darunavir	808 (18.6)	586 (18.0)	222 (20.5)	0.068
Boosted PI	1024 (23.6)	755 (23.2)	269 (24.8)	0.272
Patients having used, n (%)				
Lopinavir/ritonavir	2010 (23.5)	711 (21.9)	309 (28.5)	**<0.001**
Amprenavir	44 (1.0)	27 (0.8)	17 (1.6)	**0.035**
Atazanavir	923 (21.3)	632 (19.4)	291 (26.9)	**<0.001**
Darunavir	1069 (24.6)	771 (23.7)	298 (27.5)	**0.011**
Fosamprenavir	182 (4.2)	126 (3.9)	56 (5.2)	**0.065**
Indinavir	692 (16.0)	429 (13.2)	263 (24.3)	**<0.001**
Nelfinavir	462 (10.7)	296 (9.1)	166 (15.3)	**<0.001**
Ritonavir	1788 (41.2)	1285 (39.5)	503 (46.4)	**<0.001**
Saquinavir	431 (9.9)	313 (9.6)	118 (10.9)	0.224
Tenofovir	3670 (84.6)	2711 (83.3)	959 (88.6)	**<0.001**
Tipranavir	58 (1.3)	39 (1.2)	19 (1.8)	0.168
Any PI	2496 (57.6)	1769 (54.4)	727 (67.1)	**<0.001**
Boosted PI	2156 (49.7)	1554 (47.8)	602 (55.6)	**<0.001**
Previous/current treatment with TEN, n (%)	3670 (84.6)	2711 (83.3)	959 (88.6)	**<0.001**
Previous/current treatment with boosted PI, n (%)	2156 (49.7)	1554 (47.8)	602 (55.6)	**<0.001**
Previous/current PI or boosted PI plus TEN, n (%)	1865 (43.0)	1313 (40.4)	552 (51.0)	**<0.001**
Previous/current PI or boosted PI without TEN, n (%)	291 (6.7)	241 (7.4)	50 (4.6)	**0.001**
Previous/current NNRTI plus TEN, n (%)	2144 (49.4)	1615 (49.6)	529 (48.8)	0.654
Previous/current NNRTI without TEN, n (%)	192 (4.4)	144 (4.4)	48 (4.4)	0.992
Previous/current Integrase Inh plus TEN, n (%)	381 (8.8)	269 (8.3)	112 (10.3)	**0.037**
Previous/current Integrase Inh without TEN, n (%)	58 (1.3)	47 (1.4)	11 (1.0)	0.287
Duration of the treatment, years[a]				
Lopinavir/ritonavir	2.40 (3.8)	2.450 (3.8)	2.30 (3.8)	0.534
Amprenavir	1.50 (2.1)	1.20 (2.4)	1.75 (2.0)	0.642
Atazanavir	2.90 (4.1)	2.90 (4.1)	3.00 (3.9)	0.555
Darunavir	2.0 (2.3)	1.90 (2.3)	2.20 (2.6)	0.242
Fosamprenavir	1.90 (3.8)	1.80 (3.5)	2.30 (4.7)	0.358
Indinavir	1.70 (2.4)	1.60 (1.9)	1.90 (2.9)	**0.015**
Nelfinavir	1.80 (2.5)	2.00 (2.7)	1.70 (2.1)	0.114
Ritonavir	2.60 (4.2)	2.40 (4.0)	3.00 (4.7)	**0.002**
Saquinavir	1.80 (2.8)	2.00 (2.9)	1.70 (2.3)	0.264
Tenofovir	3.20 (4.4)	3.00 (4.1)	3.90 (4.9)	**<0.001**
Tipranavir	1.80 (2.9)	2.00 (2.8)	1.20 (2.9)	0.716
Any PI	4.00 (5.8)	3.90 (5.6)	4.30 (6.2)	**0.008**
Boosted PI	3.30 (5.0)	3.10 (4.7)	3.75 (5.2)	**0.004**

[a] Results expressed as median and interquartile range (IQR). Significant $p < 0.05$.
ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; Inh, inhibitors; TEN, tenofovir disoproxil fumarate. All PIs were boosted with ritonavir.

Caucasian patients, and ESRD was associated with a high overall mortality.[25] The overall prevalence of ESRD ranged from 0.3% to 0.5%.[20,25]

There is significant clinical information on moderate chronic renal failure (GFR < 60 mL/min) among patients with HIV-infection.[13–18,26] However, there is scant information on milder degrees of renal function impairment, especially with GFR 60–89 mL/min.[9,27] The reason is the relatively recent use of the estimated glomerular filtration rate (eGFR) with the MDRD-equation which is not validated to discriminate GFR over 60 mL/min. In addition, the eGFR with the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

Table 3 – Demographic and HIV-related characteristics according to sex.

	Female patients			*p*-value	Male patients			*p*-value	*p*-value[b]
	Global female[b]	Normal eGFR	Mildly-reduced eGFR		Global male[b]	Normal eGFR	Mildly-reduced eGFR		
Number of patients, n (%)	819	580	239 (29.2)	–	3518	2674	844 (23.9)	–	**0.002**
Age, years[a]	47 (11)	45 (11)	51 (13)	**<0.001**	44 (15)	42 (15)	50 (13)	**<0.001**	**<0.001**
Black race, n (%)	23 (5.3)	18 (5.4)	5 (4.8)	0.802	32 (1.4)	22 (1.2)	10 (2.0)	0.147	**<0.001**
Body mass index, kg/m²[a]	22.4 (5.8)	22.6 (6.5)	22.1 (4.9)	0.240	23.0 (3.3)	22.8 (3.3)	23.4 (3.1)	**0.004**	0.269
Hypertension, n (%)	112 (13.7)	58 (10.0)	54 (22.6)	**<0.001**	418 (11.9)	238 (8.9)	180 (21.3)	**<0.001**	0.158
Diabetes mellitus, n (%)	39 (4.8)	24 (4.1)	15 (6.3)	0.191	160 (4.5)	96 (3.6)	64 (7.6)	**<0.001**	0.792
Dyslipidemia, n (%)	89 (10.9)	46 (7.9)	43 (18.0)	**<0.001**	439 (12.5)	256 (9.6)	183 (21.7)	**<0.001**	0.204
Prior cardiovascular event, n (%)	21 (2.6)	12 (2.2)	8 (3.3)	0.363	147 (4.2)	84 (3.1)	63 (7.5)	**<0.001**	**0.031**
HBV coinfection, n (%)	13 (1.6)	9 (1.6)	4 (1.7)	0.979	132 (3.8)	91 (3.4)	41 (4.9)	0.236	**0.019**
HCV coinfection, n (%) (n = 4329)	268 (32.8)	176 (30.4)	92 (38.7)	**0.022**	683 (19.4)	532 (19.9)	151 (17.9)	0.196	**<0.001**
Duration of HIV infection, years[a]	17.5 (11.8)	17.0 (12.9)	17.7 (10.1)	**0.022**	9.2 (13.1)	8.4 (12.5)	12.5 (13.0)	**<0.001**	**<0.001**
HIV acquisition, n (%)									
Heterosexual	559 (68.3)	398 (68.6)	161 (67.4)	0.688	557 (15.8)	390 (14.6)	167 (19.8)	**0.001**	**<0.001**
Homosexual	25 (3.1)	19 (3.3)	6 (2.5)	0.695	2565 (72.9)	1978 (74.0)	587 (69.5)	**0.013**	**<0.001**
Drug abuse	175 (21.4)	115 (19.8)	60 (25.1)	0.229	427 (12.1)	330 (12.3)	97 (11.5)	0.710	**<0.001**
Other route	27 (3.3)	24 (4.1)	3 (1.3)	0.086	21 (0.6)	13 (0.5)	8 (0.9)	0.289	**<0.001**
Unknown	51 (6.2)	38 (6.6)	13 (5.4)	0.549	177 (5.0)	137 (5.1)	40 (4.7)	0.366	0.167
Prior AIDS events, n (%)	192 (23.4)	132 (22.8)	60 (25.1)	0.263	645 (18.3)	446 (16.7)	199 (23.6)	**<0.001**	**0.001**
HIV suppression, n (%)									
On treatment	721 (88.0)	504 (86.9)	217 (90.8)	0.199	3119 (88.7)	2321 (86.8)	798 (94.5)	**<0.001**	**0.008**
Without treatment	1 (1.5)	8 (1.4)	4 (1.7)		17 (0.5)	15 (0.6)	2 (0.2)		
No suppression	86 (10.5)	68 (11.7)	18 (7.5)		382 (10.9)	338 (12.6)	44 (5.2)		
CD4 cell count, cells/mm³[a]									
Nadir	196 (204)	207 (208)	178 (183)	**0.002**	266 (245)	277 (240)	232 (249)	**<0.001**	**<0.001**
Current	624 (406)	618 (394)	638 (434)	0.331	635 (371)	638 (369)	625 (377)	0.631	0.204
Currently on ART, n (%)	797 (97.3)	565 (97.4)	232 (97.1)	0.783	3402 (96.7)	2567 (96.0)	835 (98.9)	**<0.001**	0.369
Time under current ART regimen, years[a]	1.7 (4.2)	1.7 (4.1)	1.7 (4.6)	0.337	1.2 (3.4)	1.2 (3.3)	1.4 (3.7)	**<0.001**	
Current ART regimen, n (%)									
No treatment	22 (2.7)	15 (2.6)	7 (2.9)	0.978	116 (3.3)	107 (4.0)	9 (1.1)	**0.001**	**<0.001**
NNRTI-based	356 (43.5)	253 (43.6)	103 (43.1)		1980 (56.3)	1506 (56.3)	474 (56.2)		
PI-based	41 (5.0)	30 (5.2)	11 (4.6)		95 (2.7)	72 (2.7)	23 (2.7)		
Boosted PI-based	290 (35.4)	207 (35.7)	83 (34.7)		967 (27.5)	723 (27.0)	244 (28.9)		
Integrase inhibitor-based	105 (12.8)	72 (12.4)	33 (13.8)		334 (9.5)	244 (9.1)	90 (10.7)		
Other	5 (0.6)	3 (0.5)	2 (0.8)		26 (0.7)	22 (0.8)	4 (0.5)		
Patient currently using, n (%)									
Tenofovir	476 (58.1)	355 (61.2)	121 (50.6)	**0.005**	2349 (66.8)	1814 (67.8)	535 (63.4)	**0.017**	**<0.001**
Indinavir	0	0	0	–	0	0	0	–	–
Atazanavir	85 (10.4)	60 (10.3)	25 (10.5)	0.961	223 (6.3)	177 (6.6)	46 (5.5)	0.224	**<0.001**
Darunavir	161 (19.7)	116 (20.0)	45 (18.8)	0.701	647 (18.4)	470 (17.6)	177 (21.0)	0.026	0.402
Boosted PI	220 (26.9)	159 (27.4)	61 (25.5)	0.579	804 (22.9)	596 (22.3)	208 (24.6)	0.155	**0.015**
Previous or current treatment with tenofovir, n (%)	686 (83.8)	487 (84.0)	199 (83.3)	0.804	2984 (84.8)	2224 (83.2)	760 (90.0)	**<0.001**	0.449
Previous or current treatment with boosted PI, n (%)	496 (60.6)	347 (59.8)	149 (62.3)	0.503	1660 (47.2)	1207 (45.1)	453 (53.7)	**<0.001**	**<0.001**
PI or boosted PI plus TEN, n (%)	430 (52.5)	297 (51.2)	133 (55.6)	0.247	1435 (40.8)	1016 (38.0)	419 (49.6)	**<0.001**	**<0.001**
PI or boosted PI without TEN, n (%)	66 (8.1)	50 (8.6)	16 (6.7)	0.357	225 (6.4)	191 (7.1)	34 (4.0)	**0.001**	0.087
NNRTI plus TEN, n (%)	321 (39.2)	234 (40.3)	87 (36.4)	0.293	1823 (51.8)	1381 (51.6)	442 (52.4)	0.714	**<0.001**
NNRTI without TEN, n (%)	35 (4.3)	19 (3.3)	16 (6.7)	**0.028**	157 (4.5)	125 (4.7)	32 (3.8)	0.279	0.813
Integrase inhibitors plus TEN, n (%)	96 (11.7)	64 (11.0)	32 (13.4)	0.341	285 (8.1)	205 (7.7)	80 (9.5)	0.093	**0.001**
Integrase inhibitors without TEN, n (%)	9 (1.1)	8 (1.4)	1 (0.4)	0.230	49 (1.4)	39 (1.5)	10 (1.2)	0.554	0.510

[a] Results expressed as median and interquartile range (IQR). Significant $p < 0.05$.

[b] *p*-value for comparisons between global female and global male.

HBV, hepatitis B virus; HCV, hepatitis C virus; ART, antiretroviral; PI, protease inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; TEN, tenofovir disoproxil fumarate. All PIs were boosted with ritonavir.

Table 4 – Multivariate analysis of risk factors independently associated with mildly decreased renal function in patients with HIV-infection.

Risk factors	OR (95% CI)	*p*-value
Baseline age		
≤50 y	1.00 (reference)	–
>50 y	3.03 (2.58–3.55)	<0.001
Gender		
Male	1.00 (reference)	–
Female	1.23 (1.02–1.48)	0.031
Baseline hypertension	1.57 (1.25–1.97)	<0.001
Diabetes mellitus	0.99 (0.71–1.37)	0.955
Dyslipidemia	1.48 (1.17–1.87)	0.001
Previous cardiovascular events	0.77 (0.53–1.13)	0.186
HCV coinfection	0.84 (0.69–1.01)	0.387
Duration of HIV infection (years)[a]	1.01 (0.99–1.02)	0.283
HIV suppression		
No	1.00 (reference)	–
Yes	1.88 (1.39–2.53)	<0.001
CD4+ cell count nadir	1.00 (0.99–1.00)	0.467
Current and/or previous exposure to tenofovir[a]	1.67 (1.33–2.08)	<0.001
Current and/or previous exposure to boosted PI[b]	1.19 (1.03–1.39)	0.023

HCV, hepatitis C virus; PI, protease inhibitors.

[a] Tenofovir disoproxil fumarate.

[b] All PIs were boosted with ritonavir. Significant $p < 0.05$.

equation allows for more detailed analysis of renal function and discriminates patients with mildly reduced GFR (60–89 mL/min/1.73 m^2).[20]

In the present analysis, there was a significant prevalence of mildly reduced renal function (eGFR 60–89 mL/min/1.73 m^2) in 25% of the patients. The overall prevalence of mild renal impairment found in this study is in accordance with the rates of 25–40% found in other urban, ambulatory and well-controlled populations in the modern era of antiviral therapy.[28–30] Due to the asymptomatic character of this condition, these patients were often not recognized as having kidney disease by the caring clinicians and thus missed opportunities for early preventive measures.

The risk factors associated with the presence of mildly reduced renal function in HIV-infected patients have been poorly studied. In the last several years, there has been growing attention to sex in HIV epidemiology, prevention and treatment. Although the association of female sex and chronic kidney disease was not found in the classic EuroSida study,[31] several other publications,[32,33] including a modern prospective analysis of the large cohort from the D:A:D study,[34] have found contrary results. Several reasons may explain why female sex was a strong independent risk factor for mildly impaired renal function in the multivariate analysis. Firstly, in the present study, women presented a higher prevalence of black race and injecting drug use. Although not sex-specific, these factors may interact with sex and create a structural barrier to prevention, testing, and treatment services, as already addressed in a recent review.[35] The higher prevalence of prior AIDS events and lower nadir CD4 cell count support this affirmation, as they indicate more advanced stages of HIV-infection at diagnosis. Finally, there are sex differences in the antiretroviral pharmacokinetic parameters, and in general, women have been found to be more susceptible than men to developing ART-associated toxicities.[36] In fact, the longer duration of HIV-infection in women, and the more frequent exposure to boosted-PI with or without tenofovir disoproxil-fumarate are in accordance with this hypothesis.

Consistent with other studies,[16,26,27,33,34] older age was the most important risk factor for the occurrence of renal dysfunction. On the one hand, as HIV patients are living longer, they are also getting older. In 2013, individuals aged 55 and older comprised 26% of the people living with HIV in the USA.[37] Moreover, although much attention has been paid to preventing HIV-infection in young people, many patients are infected later in life. For example, 12.9% of newly reported cases of HIV in Western Europe in 2007 were in people aged 50 years or older.[38] On the other hand, chronic HIV-infection is associated with accelerated aging despite apparent viral control, manifested as increased genetic instability, enhanced T-cell senescence, diminished naïve T-cell regeneration, and altered intracellular communication. It is therefore, associated with early onset of diseases linked to aging, including renal impairment.[39,40]

In this cohort, coinfection with HCV was not found to be an independent risk factor for renal dysfunction. Among male patients, this condition was even regarded as a protective variable. Certainly, this topic remains an unsolved issue. A pooled analysis of more than 18,000 patients with HIV-infection found a 50% increased risk of chronic kidney disease among individuals with HCV-coinfection,[41] and a more recent meta-analysis of more than 13,000 subjects confirmed these findings.[42] However, both authors acknowledged that all the available studies were retrospective and subject to heterogeneity in the design and in the quality of data, as many confounding variables were not reported. Although some investigators have linked HCV to atherosclerosis and atherosclerotic diseases at the extra-hepatic level including kidneys,[43] and although there is an association between HCV infection and several types of glomerulonephritis,[44] the often observed association between

HCV infection and increased risk for kidney disease may still reflect confounding variables such as older age, injecting drug use, poor socioeconomic status, and exposure to nephrotoxic medications.

In this study, experiencing HIV-suppression was a strong independent risk factor for renal impairment. It is true that, on the one hand, an untreated HIV-infection may be related to acute and chronic kidney disease due to direct viral kidney injury (HIVAN and other manifestations), chronic inflammation, opportunistic infections, and their potentially nephrotoxic treatments. However, on the other hand, to achieve adequate control of HIV-infection, patients are exposed to prolonged periods on potentially nephrotoxic antiretrovirals and accumulate several adverse events.[45]

Tenofovir disoproxil-fumarate, the first-choice standard of care treatment, constitutes a risk factor even for milder grades of renal dysfunction.[16,46] The primary mechanism by which tenofovir causes renal toxicity may involve drug accumulation within proximal renal tubules, leading to mitochondrial injury and depletion. Tenofovir renal injury may present as partial or full Fanconi syndrome and acute tubular necrosis, eventually leading to tubulointerstitial scarring, which may account for the lack of reversibility of tenofovir renal toxicity in some individuals.[47] Nephrotoxicity due to protease inhibitors (PIs), mainly indinavir and atazanavir, is related to the formation of urolithiasis and intratubular precipitation, obstructive nephropathy, and acute or chronic interstitial nephritis. Ritonavir toxicity is more likely the result of drug interactions than of a direct kidney effect.[48] Other PIs such as nelfinavir, amprenavir, saquinavir, ritonavir, and darunavir have also been reported to cause urolithiasis.[49]

This finding has strong implications for clinical practice. Women and middle-aged patients are a population associated with an increased risk of alterations in renal function even in the initial stages of renal injury. This new scenario involves performing a specific clinical management in this group of patients, especially with the use of certain antiretroviral drugs with potentially nephrotoxic effects (as tenofovir disoproxil-fumarate or ritonavir-boosted protease-inhibitors), and intensifying the control of cardiovascular risk factors. Prospective studies are needed to assess whether it is possible to stabilize or reverse the mild decline of renal function in HIV-infected patients.

Our study has two limitations: first, currently most patients are being treated with tenofovir alafenamide, which can improve renal failure.[50] We have not evaluated in our study the impact of occult chronic renal failure of the switching from tenofovir disoproxil-fumarate to tenofovir alafenamide. Second, in this study protease-inhibitors were boosted with ritonavir and now cobicistat is the booster agent. We do not know if cobicistat can also enhance tenofovir tubular toxicity as ritonavir does.[50] Finally, due to the retrospective nature of the study, and due the fact that information was obtained from databases, ii should acknowledged that some information could have been missed (for example, minor information regarding hypertensive patients, once hypertension diagnosis was based on the use of antihypertensive medication).

Conclusion

This study found a 25% prevalence of already established renal impairment, albeit in the initial stages, among stable, ambulatory patients with well-controlled HIV-infection. Older subjects and female patients are the most susceptible population. Modifiable risk factors, such as hypertension and dyslipidemia, and exposure to potentially nephrotoxic antiretrovirals, such as tenofovir disoproxil-fumarate and ritonavir-boosted protease-inhibitors, were also associated with this outcome. It remains to be determined whether early interventions including antiretroviral therapy switch (tenofovir alafenamide, cobicistat) or improving comorbidities management will improve the course of mild chronic kidney disease.

Conflicts of interest

The authors declare no conflicts of interest.

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