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ORIGINAL RESEARCH

Evaluation of glomerular filtration rate in HIV-1-infected patients before and after combined antiretroviral therapy exposure*

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Background

The prevalence and factors associated with an increased risk of renal dysfunction in HIV-infected patients receiving or not receiving antiretroviral therapy (ART) have been poorly evaluated in observational settings.

Methods

Patients in the ICONA Foundation cohort with at least two creatinine values available while still ART-naïve were enrolled in the study. A logistic regression analysis was performed to identify predictors of an estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2 at baseline. The incidence and predictors of a $> 20\%$ reduction in eGFR from pre-combination ART (cART) levels (or a decrease from ≥ 90 to < 90 mL/min/1.73 m^2) were evaluated by Poisson regression.

Results

A total of 1505 patients were included in the study; 363 (24%) had eGFR < 90 mL/min/1.73 m^2 at baseline. Older patients [odds ratio (OR) 1.58 per 10 years older; $P < 0.00001$], female patients (OR 2.41 *vs.* male patients; $P < 0.00001$), those who had diabetes and/or hypertension (OR 2.36 *vs.* neither; $P < 0.03$) and patients with higher baseline CD4 count (OR 1.06 per 100 cells/μL higher; $P < 0.03$) showed a greater risk of eGFR < 90 mL/min/1.73 m^2. Ninety-six patients experienced an eGFR decrease of $> 20\%$ from pre-cART levels (6.8 per 100 person-years). Older age [relative risk (RR) 1.41 per 10 years older; $P = 0.005$], female gender (RR 2.25 *vs.* male; $P = 0.003$) and current exposure to didanosine (ddI), tenofovir and protease inhibitors were the major determinants.

Conclusions

We observed a relatively high rate of mild renal dysfunction in the absence of ART. In addition to traditional risk factors such as older age and diabetes/hypertension, female gender and current use of ddI, tenofovir and protease inhibitors were associated with a greater risk of decreased renal function as measured by eGFR.

Keywords: antiretroviral exposure, estimated glomerular filtration rate (eGFR), renal impairment

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†See Appendix.

Introduction

Prior to the introduction of highly active antiretroviral therapy (HAART), HIV-associated nephropathy (HIVAN) represented the most frequent cause of renal disease in

HIV-infected patients and the most important cause of end-stage renal disease (ESRD) in black Americans [2,3]. The widespread introduction of cART has resulted in a dramatic reduction in the incidence of AIDS and death in individuals with HIV infection [4] and a reduction in the risk of developing HIVAN of up to 60% [5,6].

While a direct role of HIV infection in the risk of developing nephropathy has been demonstrated [7–11], there are a number of other factors potentially influencing the onset of renal disorders through different mechanisms, whose prevalence may be different in an HIV-positive population compared with the general population. Indeed, patients' longer survival following the introduction of cART may be considered as an additional risk for renal dysfunction, as long-term toxic events associated with the prolonged used of ART have been observed (e.g. metabolic alterations, diabetes, hypertension and cardiovascular events) [12–14]. It has been hypothesized that antiretroviral medications may have a direct effect in increasing the risk of renal dysfunction, and a variety of cART-related effects, including proteinuria, renal tubular damage, interstitial nephritis and overall declines in glomerular filtration rates, have been noted [15–23].

The potential role of tenofovir in renal toxicity is a current clinical research question. As a consequence of its tolerability, convenient dosing and efficacy, this nucleoside reverse transcriptase inhibitor (NRTI) has been widely used as a component of cART regimens. There are contradictory data on tenofovir-related damage: from documented damage in early reports [24–27] to a marked lack of renal toxicity in randomized placebo-controlled trials [28–31]; moreover, toxicity was found to be increased when tenofovir was given with ritonavir-boosted protease inhibitors (PI/r) compared with tenofovir given with nonnucleoside reverse transcriptase inhibitors (NNRTIs) or cART that did not include tenofovir [32]. A mechanism involving an interaction between tenofovir and PIs/r resulting in an increased risk of renal damage has been suggested [33].

As both HIV infection and cART exposure have been associated with the development of acute and chronic renal disease, it is essential to assess the occurrence of renal dysfunction and factors related to its development in large populations of HIV-infected patients both before initiation of cART and during exposure to different cART regimens. The aim of our study was therefore to describe the prevalence of renal dysfunction and associated predictors in a large cohort of HIV-infected patients enrolled when they were still ART-naïve. Moreover, in patients who started cART during follow-up, we investigated the incidence and predictors of worsening of renal function, with focus on the role of exposure to specific antiretrovirals.

Methods

Patients

The ICONA Foundation Study is an Italian multicentre prospective observational cohort study of HIV-1-positive persons enrolled since 1997. Eligible patients are those who, for whatever reason, were naïve to antiretroviral drugs at the time of enrolment. Demographic, pre-enrolment, clinical and laboratory data and information on the specific therapies are collected for all participants and recorded online (www.iconafoundation.it). All data are updated at the occurrence of any clinical event and, in the absence of such an event, at least every 6 months. Immunovirological parameters and serological test results for hepatitis C virus antibody (HCV-Ab) and hepatitis B virus surface antigen (HBsAg) and antibody (HBsAb) are systematically recorded every 6 months; serum creatinine became part of the 6-monthly routine screening after the year 2000. Plasma HIV RNA has been measured using quantitative reverse transcriptase–polymerase chain reaction (RT-PCR; Amplicor, Roche Molecular System, Pleasanton, CA, USA), a signal ampli® cation branched DNA assay (Quantiplex; Chiron, Emeryville, CA, USA) or nucleic acid sequence-based ampli® cation (NASBA Organon Teknika, Boxtel, the Netherlands). The lower limit of detection of these assays is 500 HIV-1 RNA copies/mL. Ultrasensitive versions (with a lower limit of detection of 50 copies/mL) have been used when appropriate, starting from May 1998. CD4 cell counts are obtained using standard flow cytometry techniques.

Creatinine is measured using commercial assays (upper limit of normal 1.3 mg/dL).

Further details regarding the design and data collection are given elsewhere [34]. For this analysis, we included only patients of Italian origin for whom at least two creatinine values, obtained after January 1, 2000 while the patient was still ART-naïve, were available.

Statistical analysis

Patient selection

Included and excluded patients were compared in terms of their demographic and clinical characteristics at enrolment.

Characteristics of study population according to the estimated glomerular filtration rate (eGFR) at baseline and factors associated with an abnormal value

The eGFR was used to identify patients in the cohort with potential renal dysfunction. The estimate was calculated using the Modification of Diet in Renal Diseases (MDRD)

formula [35]:

$$\text{eGFR (MDRD)} = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742\,(\text{if female}) \times 1.212\,(\text{if black})$$

Because ethnicity is not collected in the database, only patients who were born in Italy were included in the current study and the ethnicity adjustment of the MDRD formula was omitted under the assumption that nobody was of black ethnicity.

Although the MDRD equation has not been independently validated in populations of HIV-infected patients, we have chosen this method and not others because the MDRD estimation of eGFR has been widely used in routine clinical practice and has been specifically recommended by the Infectious Diseases Society of America Guidelines for the assessment of renal function in HIV-infected patients [36].

Baseline was defined as the date of the first of the two consecutive creatinine values after January 2000, while the patient was still ART-naïve. Patients were defined as having an abnormal eGFR value at baseline if both of these two consecutive values were <90 mL/min per 1.73 m^2. The prevalence of patients with an abnormal eGFR value at baseline was calculated and the characteristics of these patients were compared with those of patients with normal eGFR (≥ 90 mL/min per 1.73 m^2) using the χ^2 test and the Wilcoxon test for independent samples.

Univariable and multivariable logistic regressions were used to determine the factors associated with the risk of having an abnormal eGFR at baseline. The following covariates were included in the model: age, gender, mode of HIV transmission, history of diabetes and/or hypertension prior to baseline, baseline CD4 cell count, baseline CD8 cell count, baseline HIV plasma viraemia, HCV/HBV coinfection and cirrhosis (HIV monoinfected, HCV/HBV-coinfected with cirrhosis, and HCV/HBV-coinfected without cirrhosis). Coinfection was established on the basis of the tests performed up to the baseline date. Patients were defined as HCV positive if anti-HCV was detected at least once before baseline and HBV positive if they were confirmed HBsAg positive for a period of at least 6 months prior to baseline. Only clinical diagnoses of cirrhosis were used to determine whether coinfection was accompanied by cirrhosis.

All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Incidence and predictors of worsening of renal function after starting cART

In order to evaluate the possible impact of cART on renal function, we performed a longitudinal analysis using only data for those patients of our study population who started cART at some point after enrolment and for whom creatinine had been measured on at least one visit after cART initiation. The date of confirmed eGFR reduction from pre-cART levels was defined *a priori* as the date of the first of two consecutive measures that were $>20\%$ lower than the pre-cART value (calculated as the average of two pre-cART values). We determined the incidence of a confirmed $>20\%$ eGFR reduction from baseline using a person-years analysis. Person-years at risk were calculated from the date of starting cART until the date of the last available creatinine measure or the date of $>20\%$ eGFR reduction from baseline, whichever occurred first. Only person-years of follow-up in which patients were receiving at least one drug were included. Standard Poisson regression was used for the univariable and multivariable analyses to identify the predictors of the development of the event. In order to test whether the use of a specific NRTI pair was associated with a 20% reduction of eGFR from baseline, we included in the models a time-dependent covariate indicating which NRTI pair the patient was currently receiving. These groups were created using the NRTI pairs that were most frequently used at the time of the event and for which a minimum of 10 person-years of usage was observed. Other covariates included were: age, gender, mode of HIV transmission, HCV/HBV coinfection, prior history of diabetes and/or hypertension (fitted as a time-dependent binary covariate: yes/no), the class of the currently received third drug (ritonavir-boosted non-indinavir PI, single non-indinavir PI, NRTI or NNRTI), baseline eGFR, baseline CD4 cell count and plasma HIV-RNA (also fitted as continuous variables), AIDS diagnosis prior to cART initiation, year of starting cART and clinical centre.

In order to assess the robustness of our defined outcome, the alternative cut-offs of 10% and 30% reductions were evaluated. Furthermore, in the subset of patients with an eGFR pre-cART ≥ 90 mL/min per 1.73 m^2, the time of a confirmed eGFR reduction from pre-cART levels was alternatively defined as the date of the first of two consecutive eGFR values <90 mL/min per 1.73 m^2. Poisson regression analyses including the same variables as were included in the main analysis were employed to identify independent predictors of a reduction of eGFR.

Results

Characteristics of the patients selected for the analysis

Patients included in the analysis ($n = 1505$) showed significant differences in immunovirological variables compared with excluded patients ($n = 5762$; Table 1);

Table 1 Characteristics of patients included and excluded from the analysis

Characteristics	Excluded	Included	*P*-value†
Number of patients	5762	1505	
Age (years) [median (IQR)]	39 (34, 45)	38 (33, 43)	0.000001
Female gender [*n* (%)]	1631 (28.3)	423 (28.1)	0.88
Mode of HIV transmission [*n* (%)]			0.02
IDU	2019 (35.0)	435 (28.9)	
Homosexual contacts	1255 (21.8)	421 (28.0)	
Heterosexual contacts	2104 (36.5)	575 (38.2)	
Other/unknown	384 (6.7)	74 (4.9)	
HBsAg [*n* (%)]			0.000001
Negative	3089 (53.6)	1198 (79.6)	
Positive	77 (1.3)	16 (1.1)	
Not tested	2596 (45.1)	291 (19.3)	
HCV-Ab [*n* (%)]			0.000001
Negative	1968 (34.2)	763 (50.7)	
Positive	1137 (19.7)	429 (28.5)	
Not tested	2657 (46.1)	313 (20.8)	
Hepatitis* [*n* (%)]			0.000001
No	1897 (32.9)	731 (48.6)	
Yes; cirrhosis free	1125 (19.5)	432 (28.7)	
Yes; with cirrhosis	56 (1.0)	8 (0.5)	
Not tested	2684 (46.6)	334 (22.2)	
Diabetes or hypertension [*n* (%)]			0.002
Yes	61 (1.1)	32 (2.1)	
CD4 count (cells/μL) [median (IQR)]	450 (273, 665)	505.0 (356, 680)	0.000001
CD8 count (cells/μL) [median (IQR)]	921 (647, 1270)	936.5 (676, 1300)	0.16
Viral load (log_{10} copies/mL) [median (IQR)]	3.00 (1.70, 4.42)	4.14 (3.36, 4.72)	0.000001

*Hepatitis C virus antibody (HCV-Ab) positive or hepatitis B virus surface antigen (HBsAg) positive.
†χ^2 or Wilcoxon test as appropriate.
IDU, injecting drug use; IQR, interquartile range.

included patients had higher CD4 cell counts (505 *vs.* 450 cells/μL, respectively; $P<0.0001$) and higher median HIV RNA levels (4.14 *vs.* 3.00 $\log_{10}$ HIV-1 RNA copies/mL, respectively; $P<0.0001$) at baseline. Included patients were younger (38 *vs.* 39 years, respectively; $P<0.0001$) and more likely to be affected by diabetes and/or hypertension (2% *vs.* 1%, respectively; $P=0.02$); a lower percentage of included patients acquired HIV infection thorough injecting drug use (29% of the included patients *vs.* 35% of the excluded patients). There were no clinical differences in the percentage of female patients or CD8 cell count.

Characteristics of the study population according to eGFR at baseline and factors associated with an abnormal value

A total of 1505 patients satisfied the inclusion criteria for the cross-sectional analysis. The clinical and immunovirologic characteristics of the patients, stratified by eGFR at baseline (<90 or ≥ 90 mL/min/1.73 m^2), are summarized in Table 2. A confirmed eGFR <90 mL/min/1.73 m^2 was observed in 363 (24%) of the patients. Of these, 353 (97%) had an eGFR in the range of 60–89 mL/min/1.73 m^2, while only 10 patients (3%) had an eGFR of 30–59 mL/min/1.73 m^2 and none had an eGFR below 30 mL/min/1.73 m^2.

In univariable analysis, compared with patients with normal eGFR, patients with a value of eGFR <90 mL/min/1.73 m^2 at baseline were older, had higher CD4 cell counts, and were more likely to be female and to have suffered from diabetes and/or hypertension prior to baseline; in contrast, patients with normal eGFR were more likely to be coinfected with hepatitis B or C virus (Table 2).

After adjustment, older age [odds ratio (OR) 1.58 per 10 years older; 95% confidence interval (CI) 1.37–1.82], female gender (OR 2.41 *vs.* male; 95% CI 1.75–3.31), a prior history of diabetes and/or hypertension (OR 2.36 *vs.* neither; 95% CI 1.08–5.14), baseline CD4 count (OR 1.06 per 100 cells/μL higher; 95% CI 1.01–1.11) and hepatitis coinfection (OR 0.51 *vs.* HIV monoinfection; 95% CI 0.34–0.78) were the sole independent predictors of a value <90 mL/min/1.73 m^2 at baseline (Table 2).

Incidence and predictors of worsening of renal function after starting cART

A total of 644 patients (43% of the total studied) started cART at some point during follow-up and were included in the longitudinal analysis (Table 3). The median calendar year of cART initiation was 2005 (range 2000–2009) and the median number of creatinine values post cART was 6 [interquartile range (IQR) 2–10]. There was no evidence that the frequency of creatinine measurements post cART in patients with eGFR <90 mL/min/1.73 m^2 (median per year 6; IQR 3–10) was different from that in patients with normal eGFR (median per year 6; IQR 2–10; Wilcoxon *P*-value = 0.12).

The most frequently used NRTI pairs were tenofovir/emtricitabine (24%) and zidovudine/lamivudine (22%); 48% of the person-years of follow-up (PYFU) was spent on an NNRTI-containing regimen, 28% on a ritonavir-boosted PI-containing regimen (not including indinavir) and 11% on a single-PI-containing regimen (not including indinavir) (Table 3).

Over 1412 person years of follow-up (PYFU) while patients were receiving at least one antiviral drug, we observed 96 events (confirmed eGFR decrease ≥ 20% from pre-cART levels), resulting in a crude incidence rate of 6.8 per 100 PYFU (95% CI 5.5–8.2). Factors independently associated with a ≥ 20% decrease in eGFR were female gender [relative risk (RR) 2.25 *vs.* male; 95% CI 1.32–3.84] and older age (RR 1.41 per 10 years older; 95% CI 1.11–1.79);

Table 2 Patient characteristics according to estimated glomerular filtration rate (eGFR) at baseline and factors associated with an eGFR < 90 mL/min per 1.73 m^2 at baseline from fitting a logistic regression model

Characteristic	eGFR ≥ 90 mL/min/1.73 m^2	eGFR < 90 mL/min/1.73 m^2	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Number of patients	1142	363				
Age (years)						
Median (IQR)	38 (32, 43)	40 (36, 46)				
Per 10 years older			1.50 (1.32, 1.71)	0.000001	1.58 (1.37, 1.82)	0.000001
Gender [*n* (%)]						
Male	858 (75.1)	224 (61.7)	1.00		1.00	
Female	284 (24.9)	139 (38.3)	1.87 (1.46, 2.41)	0.000001	2.41 (1.75, 3.31)	0.000001
Mode of HIV transmission [*n* (%)]						
IDU	347 (30.4)	88 (24.2)	0.67 (0.50, 0.90)	0.008	1.16 (0.77, 1.75)	0.48
Homosexual contacts	321 (28.1)	100 (27.5)	0.82 (0.62, 1.10)	0.19	1.27 (0.88, 1.84)	0.20
Heterosexual contacts	417 (36.5)	158 (43.5)	1.00		1.00	
Other/unknown	57 (5.0)	17 (4.7)	0.79 (0.44, 1.39)	0.41	0.90 (0.48, 1.71)	0.75
Hepatitis* [*n* (%)]						
No	530 (46.4)	201 (55.4)	1.00		1.00	
Yes; cirrhosis free	354 (31.0)	78 (21.5)	0.58 (0.43, 0.78)	0.0003	0.51 (0.34, 0.78)	0.002
Yes; with cirrhosis	6 (0.5)	2 (0.6)	0.88 (0.18, 4.39)	0.88	0.47 (0.05, 4.22)	0.50
Not tested	252 (22.1)	82 (22.6)	0.86 (0.64, 1.16)	0.31	0.80 (0.57, 1.13)	0.21
Diabetes or hypertension [*n* (%)]						
No	1125 (98.5)	348 (95.9)	1.00		1.00	
Yes	17 (1.5)	15 (4.1)	2.85 (1.41, 5.77)	0.004	2.36 (1.08, 5.14)	0.03
CD4 count (cells/μL)						
Median (IQR)	497 (351, 670)	537 (377, 704)				
Per 100 cells/μL higher			1.04 (1.00, 1.08)	0.04	1.06 (1.01, 1.11)	0.03
CD8 count (cells/μL)						
Median (IQR)	918 (672, 1271)	1008 (691, 1333)				
Per 100 cells/μL higher			1.01 (0.99, 1.03)	0.25	1.01 (0.99, 1.03)	0.45
Viral load (log_{10} copies/mL)						
Median (IQR)	4.14 (3.35, 4.73)	4.13 (3.41, 4.67)				
Per log_{10} copies/mL higher			0.99 (0.88, 1.10)	0.81	1.05 (0.92, 1.20)	0.50

*Hepatitis C virus antibody (HCV-Ab) positive or hepatitis B virus surface antigen (HBsAg) positive.
CI, confidence interval; IDU, injecting drug use; IQR, interquartile range; OR, odds ratio.

compared with patients treated with zidovudine/lamivudine, those currently receiving tenofovir/emtricitabine (RR 4.78; 95% CI 2.19–10.43), tenofovir/lamivudine (RR 4.20; 95% CI 1.95–9.02) or didanosine/emtricitabine (RR 11.88; 95% CI 2.27–62.18) appeared to be at increased risk of a decrease in eGFR. Similarly, patients on a PI-containing cART (even after exclusion of indinavir) were at increased risk compared with those receiving NNRTI-containing ART (RR 3.18; 95% CI 1.62–6.23 if on an old, single-PI regimen and RR 2.15; 95% CI 1.25–3.70 if on a ritonavir-boosted regimen), although, interestingly, patients receiving NRTIs alone were those at the highest risk (RR 9.39; 95% CI 1.79–49.42; Table 4). After controlling for the most recent CD4 cell count and viral load (as opposed to the baseline values), results were similar; in addition to the confirmed association with female gender and age, the following RR values were estimated for the comparison of NRTI pairs to zidovudine/lamivudine: tenofovir/emtricitabine, RR 4.86 (95% CI 2.28–10.34); tenofovir/lamivudine, RR 4.64 (95% CI 2.22–9.68), and didanosine/emtricitabine, RR 7.68 (95% CI 1.52–38.66); and for the third drug class compared to NNRTIs: RR 4.33 (95% CI 2.24–8.35) for a single PI; RR 2.46 (95% CI 1.48–4.08) for PIs/r, and RR 11.9 (95% CI 2.09–67.48) for NRTIs alone. Results were similar in sensitivity analyses using the alternative cut-offs of 10% and 30% reductions from pre-cART levels (data not shown).

In 437 patients who had a value of eGFR > 90 mL/min/1.73 m^2 at the time of starting cART (68% of the total 644 who started cART), the median eGFR value was 109 mL/min/1.73 m^2 (IQR 99–121 mL/min/1.73 m^2). In this subset, we observed 104 patients who experienced a decrease in eGFR to a value of < 90 mL/min/1.73 m^2 over a total of 846 PYFU for a crude incidence rate of 12.3 per 100 PYFU (95% CI 10.2–14.7). Independent predictors of this outcome were similar to those identified in the main analysis (female gender, older age and use of NRTIs, especially tenofovir and didanosine; Table 5).

Discussion

In our study, conducted in a large cohort of HIV-infected patients who were enrolled when ART-naïve, we aimed to describe the prevalence and the predictors of impaired

Table 3 Characteristics of patients who started combination antiretroviral therapy (cART), and usage of nucleoside reverse transcriptase inhibitor (NRTI) pairs during follow-up

Characteristic at cART initiation	(*n* = 644)
Age (years) [median (IQR)]	39.00 (33.50, 44.00)
Female gender [*n* (%)]	193 (30.0)
Mode of HIV transmission [*n* (%)]	
IDU	182 (28.3)
Homosexual contacts	161 (25.0)
Heterosexual contacts	274 (42.5)
Other/unknown	27 (4.2)
HCV-Ab [*n* (%)]	
Negative	344 (53.4)
Positive	178 (27.6)
Not tested	122 (18.9)
Diabetes or hypertension [*n* (%)]	
Yes	18 (2.8)
CD4 count (cells/μL) [median (IQR)]	295.0 (222.5, 391.0)
Viral load (log_{10} copies/mL) [median (IQR)]	4.69 (3.89, 5.11)

Antiretroviral drugs	Person-years of use (*n* = 1522)
Off ART [*n* (%)]*	110 (7.2)
NRTI pair [*n* (%)]*	
Tenofovir/emtricitabine	369 (24.3)
Tenofovir/lamivudine	197 (12.9)
Abacavir/lamivudine	130 (8.5)
Tenofovir/stavudine	11 (0.7)
Stavudine/lamivudine	25 (1.7)
Didanosine/emtricitabine	9 (0.6)
Didanosine/tenofovir	23 (1.5)
Didanosine/lamivudine	68 (4.5)
Didanosine/stavudine	17 (1.1)
Zidovudine/tenofovir	10 (0.6)
Zidovudine/lamivudine	335 (22.0)
Other pair	9 (0.6)
Other NRTI use	210 (13.8)
Third drug/drug class [*n* (% of 1412 PYFU on ART)]	
NRTIs only	181 (12.8)
Non-indinavir single PI	152 (10.8)
Non-indinavir PI/r	389 (27.5)
Indinavir (single or ritonavir-boosted)	8 (0.6)
NNRTI	683 (48.4)

*Person-years (percentage of total).
HCV-Ab, hepatitis C virus antibody; IDU, injecting drug use; IQR, interquartile range; PI, protease inhibitor; r, ritonavir; NNRTI, nonnucleoside reverse transcriptase inhibitor.

renal function in drug-naïve patients and in those who subsequently started cART.

The finding that, according to our definition, a quarter of the drug-naïve HIV-infected patients of our cohort showed renal function abnormalities confirmed that mild renal function impairment is relatively frequent in HIV-positive untreated individuals, although severe reductions in eGFR have been observed only in a small subset of patients.

HIV-infected patients have been demonstrated in other studies to have an increased incidence of acute renal failure as compared with uninfected patients, in both the pre-highly active ART (HAART) and post-HAART eras [37–40], and the analysis of our large cohort adds further elements to the understanding of the epidemiological features of renal dysfunction in HIV-positive drug-naïve subjects. As previously described [41–42], traditional risk factors associated with renal damage in the HIV-negative population, such as female gender, older age, and diabetes and/or hypertension, as well as CD4 cell count, were associated with a greater risk of a low eGFR value while patients remained untreated. This finding seems to support the view that ageing and metabolic complications in HIV-positive populations are additional factors to consider in the clinical management of these patients [40–42].

Despite the fact that several analyses have shown the potentially beneficial role of cART in reducing the incidence of chronic renal disease and in the treatment and prevention of HIVAN, multiple reports have also indicated that cART appears to be responsible for renal damage and that patients with renal function decline are more likely to have received cART than patients with normal renal function. Nevertheless, beyond simply identifying the existence of this potential toxicity, the key clinical questions are which patients are at the highest risk of renal dysfunction and what is the best time to monitor the emergence of this toxicity. The answers to these questions remain largely unknown because the relationship between the development and progression of renal dysfunction and cART exposure in HIV-infected patients is currently poorly understood [36–42].

In our longitudinal analysis, we observed an incidence rate of seven per 100 PYFU for a decrease in eGFR of at least 20% from pre-ART levels in patients on ART who were drug-naïve at baseline. In the analysis of patients who initiated cART, female gender and older age remained associated with a higher risk of eGFR decline from pre-ART values while a history of diabetes or hypertension before cART was no longer predictive of a worse outcome. Regarding the comparison between antiretrovirals, compared with zidovudine/lamivudine usage, current use of NRTI pairs containing tenofovir (with either emtricitabine or lamivudine) or didanosine (with emtricitabine alone) was associated with a higher risk of eGFR reduction, and so was the use of a PI (single or ritonavir-boosted) as compared to an NNRTI. Our findings were similar when a number of alternative definitions of eGFR decrease were used and are consistent with those of other recent studies showing that patients receiving tenofovir in combination with PI/r-based regimens had an increased decline in renal function compared with those receiving tenofovir/NNRTI or non-tenofovir-treated individuals [15–33].

This study has several limitations. eGFR values were not adjusted for potential exposure to possibly nephrotoxic drugs such as aminoglycosides or drugs used for the

Table 4 Factors associated with a decrease of >20% from the pre-antiretroviral therapy (ART) value in a Poisson regression analysis [all patients starting combination ART (cART)]

Characteristics	Crude RR (95% CI)	*P*-value	Adjusted RR (95% CI)[†]	*P*-value
Age (years)				
Per 10 years older	1.11 (0.91, 1.35)	0.31	1.41 (1.11, 1.79)	0.005
Gender				
Male	1.00		1.00	
Female	1.22 (0.80, 1.86)	0.35	2.25 (1.32, 3.84)	0.003
Mode of HIV transmission				
Heterosexual contacts	1.00		1.00	
IDU	1.04 (0.65, 1.69)	0.86	0.59 (0.30, 1.16)	0.13
Homosexual contacts	0.76 (0.44, 1.32)	0.33	1.31 (0.66, 2.58)	0.44
Other/unknown	1.34 (0.57, 3.14)	0.50	2.23 (0.83, 6.00)	0.11
Hepatitis coinfection*				
Negative	1.00		1.00	
Positive	1.50 (0.95, 2.36)	0.08	1.65 (0.86, 3.20)	0.13
Not tested	1.20 (0.71, 2.04)	0.49	1.28 (0.69, 2.38)	0.43
Diabetes or hypertension				
No	1.00		1.00	
Yes	1.55 (0.57, 4.21)	0.39	1.65 (0.54, 5.05)	0.38
Baseline CD4 count (cells/μL)				
Per 100 cells/μL higher	0.91 (0.81, 1.04)	0.16	0.94 (0.83, 1.07)	0.36
Baseline viral load (log_{10} copies/mL)				
Per log_{10} copies/mL higher	1.24 (1.01, 1.54)	0.045	1.13 (0.89, 1.44)	0.30
Baseline eGFR (mL/min/1.73 m^2)				
Per 10 mL/min/1.73 m^2 higher	1.34 (1.24, 1.45)	0.000001	1.43 (1.30, 1.57)	0.000001
NRTI pair				
Zidovudine/lamivudine	1.00		1.00	
Tenofovir/emtricitabine	3.06 (1.63, 5.73)	0.0005	4.78 (2.19, 10.43)	0.00008
Tenofovir/lamivudine	3.09 (1.55, 6.17)	0.001	4.20 (1.95, 9.02)	0.0002
Abacavir/lamivudine	1.11 (0.40, 3.13)	0.84	1.88 (0.63, 5.65)	0.26
Stavudine/lamivudine	2.28 (0.51, 10.09)	0.28	2.06 (0.26, 16.34)	0.49
Didanosine/emtricitabine	6.55 (1.48, 29.02)	0.01	11.88 (2.27, 62.18)	0.003
Didanosine/lamivudine	0.85 (0.19, 3.75)	0.83	1.81 (0.38, 8.59)	0.46
Didanosine/stavudine	1.68 (0.22, 12.82)	0.62	2.54 (0.31, 20.46)	0.38
Other NRTI use[‡]	1.51 (0.68, 3.37)	0.31	0.43 (0.07, 2.55)	0.36
Third drug/drug class				
NNRTI	1.00		1.00	
Non-indinavir single PI	2.58 (1.42, 4.67)	0.002	3.18 (1.62, 6.23)	0.0008
Non-indinavir PI/r	2.19 (1.35, 3.55)	0.001	2.15 (1.25, 3.70)	0.006
NRTIs only	1.53 (0.78, 2.98)	0.22	9.39 (1.79, 49.32)	0.008

*Hepatitis C virus antibody (HCV-Ab) positive or hepatitis B virus surface antigen (HBsAg) positive.
[†]Also adjusted for AIDS and calendar year of starting ART.
[‡]Single NRTI or three NRTIs or more.
CI, confidence interval; eGFR, estimated glomerular filtration rate; IDU, injecting drug use; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir; RR, relative risk.

treatment of opportunistic infections. The MDRD equation has not been independently validated in populations of HIV-infected patients and our analysis was not repeated using alternative methods of estimation (e.g. the Cockcroft–Gault, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Mayo Quadratic or Schwartz formulas) [43–45]. Moreover, because data were collected in an observational setting, patients were not randomized to treatment and channelling bias cannot be ruled out.

In conclusion, our study shows that, in our study population of untreated HIV-infected patients, moderate renal dysfunction (eGFR < 90 mL/min/1.73 m^2) is relatively frequent (25%) while severe impairment (eGFR < 60 mL/min/1.73 m^2) is rare (3%). Moreover, we provide further evidence supporting the hypothesis that current use of specific antiretrovirals (didanosine-, tenofovir- and PI-containing therapies) may result in an increased risk of eGFR decline in HIV-infected patients beginning cART. For some of the drug combinations studied, the association with the risk of developing the outcome was of similar strength to that seen for older age. Although our definition of eGFR decline ($\geq$ 20% decline from pre-therapy levels) might be regarded as a relatively small decrease, we consider it paramount to monitor renal function in HIV-infected patients receiving or not receiving ART, as the progressive worsening of renal function may in the long

Table 5 Factors associated with a decrease to <90 mL/min/1.73 m^2 after starting combination antiretroviral therapy (cART) in a Poisson regression analysis (only for patients with a pre-ART value ≥ 90 mL/min/1.73 m^2)

Characteristics	Crude RR (95% CI)	*P*-value	Adjusted† RR (95% CI)	*P*-value
Age (years)				
Per 10 years older	1.30 (1.09, 1.57)	0.004	1.28 (1.04, 1.57)	0.021
Gender				
Male	1.00		1.00	
Female	1.54 (1.02, 2.32)	0.04	2.02 (1.22, 3.34)	0.006
Mode of HIV transmission				
Heterosexual contacts	1.00		1.00	
IDU	0.56 (0.34, 0.92)	0.02	0.56 (0.29, 1.09)	0.09
Homosexual contacts	0.96 (0.60, 1.52)	0.85	1.35 (0.75, 2.43)	0.31
Other/unknown	0.85 (0.31, 2.36)	0.76	1.43 (0.47, 4.38)	0.53
Hepatitis coinfection*				
Negative	1.00		1.00	
Positive	0.70 (0.44, 1.10)	0.12	1.20 (0.65, 2.24)	0.56
Not tested	0.75 (0.46, 1.25)	0.27	1.01 (0.58, 1.78)	0.96
Diabetes or hypertension				
No	1.00		1.00	
Yes	2.14 (0.53, 8.69)	0.29	5.92 (1.30, 27.01)	0.022
Baseline CD4 count (cells/μL)				
Per 100 cells/μL higher	0.94 (0.84, 1.06)	0.31	1.02 (0.91, 1.16)	0.70
Baseline viral load ($\log_{10}$ copies/mL)				
Per $\log_{10}$ copies/mL higher	1.15 (0.96, 1.39)	0.14	1.17 (0.95, 1.44)	0.14
Baseline eGFR (mL/min/1.73 m^2)				
Per 10 mL/min/1.73 m^2 higher	0.69 (0.59, 0.81)	0.00001	0.66 (0.55, 0.78)	0.000001
NRTI pair				
Zidovudine/lamivudine	1.00		1.00	
Tenofovir/emtricitabine	2.81 (1.57, 5.02)	0.0005	3.56 (1.76, 7.21)	0.0004
Tenofovir/lamivudine	2.00 (1.03, 3.88)	0.04	1.62 (0.79, 3.31)	0.18
Abacavir/lamivudine	2.29 (1.04, 5.04)	0.04	1.94 (0.83, 4.55)	0.13
Stavudine/lamivudine	0.84 (0.11, 6.32)	0.86	0.82 (0.10, 6.91)	0.86
Didanosine/emtricitabine	4.32 (0.99, 18.81)	0.05	5.34 (1.12, 25.46)	0.04
Didanosine/lamivudine	0.78 (0.18, 3.41)	0.75	1.05 (0.23, 4.85)	0.95
Other NRTI use‡	1.77 (0.88, 3.59)	0.11	0.38 (0.08, 1.80)	0.22
Third drug/drug class				
NNRTI	1.00		1.00	
Non-indinavir single PI	1.86 (0.97, 3.59)	0.06	1.96 (0.95, 4.04)	0.07
Non-indinavir PI/r	2.10 (1.34, 3.29)	0.001	2.02 (1.23, 3.32)	0.006
NRTIs only	1.72 (0.95, 3.11)	0.07	7.67 (1.77, 33.33)	0.007

*Hepatitis C virus antibody (HCV-Ab) positive or hepatitis B virus surface antigen (HBsAg) positive.
†Also adjusted for AIDS, calendar year of starting ART and frequency of monitoring.
‡Single NRTI or three NRTIs or more.
CI, confidence interval; eGFR, estimated glomerular filtration rate; IDU, injecting drug use; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir; RR, relative risk.

term reach a clinically significant level. We also consider close monitoring to be important in view of the fact that (i) newly diagnosed HIV-infected subjects tend to be older and (ii) HIV-infected populations are ageing as the use of ART has led to patients living longer and thus being at increased risk of metabolic and cardiovascular complications.

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Appendix: ICONA Foundation Study Group

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