Hepatitis C virus viremia increases the incidence of chronic kidney disease in HIV-infected patients

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Background: Several studies have reported on an association between hepatitis C virus (HCV) antibody status and the development of chronic kidney disease (CKD), but the role of HCV viremia and genotype are not well defined.

Methods: Patients with at least three serum creatinine measurements after 1 January 2004 and known HCV antibody status were included. Baseline was defined as the first eligible estimated glomerular filtration rate (eGFR) (Cockcroft–Gault equation), and CKD was either a confirmed (>3 months apart) eGFR of 60 ml/min per 1.73 m^2 or less for patients with a baseline eGFR more than 60 ml/min per 1.73 m^2 or a confirmed 25% decline in eGFR for patients with a baseline eGFR of 60 ml/min per 1.73 m^2 or less. Incidence rates of CKD were compared between HCV groups (anti-HCV-negative, anti-HCV-positive with or without viremia) using Poisson regression.

Results: Of 8235 patients with known anti-HCV status, 2052 (24.9%) were anti-HCV-positive of whom 983 (47.9%) were HCV-RNA-positive, 193 (9.4%) HCV-RNA-negative and 876 (42.7%) had unknown HCV-RNA. At baseline, the median eGFR was 97.6 (interquartile range 83.8–113.0) ml/min per 1.73 m^2. During 36123 person-years of follow-up (PYFU), 495 patients progressed to CKD (6.0%) with an incidence rate of 14.5 per 1000 PYFU (95% confidence interval 12.5–14.9). In a multivariate Poisson model, patients who were anti-HCV-positive with HCV viremia had a higher incidence rate of CKD, whereas patients with cleared HCV infection had a similar incidence rate of CKD compared with anti-HCV-negative patients. There was no association between CKD and HCV genotype.

Conclusion: Compared with HIV-monoinfected patients, HIV-positive patients with chronic rather than cleared HCV infection were at increased risk of developing CKD, suggesting a contribution from active HCV infection toward the pathogenesis of CKD.

AIDS 2012, **26**:1917–1926

Keywords: coinfection, hepatitis C virus, HIV, kidney disease, viremia

Introduction

Although the introduction of combination antiretroviral (ARV) treatment (cART) has resulted in a decrease in HIV-associated nephropathy, chronic kidney disease (CKD) remains an important cause of morbidity and mortality in HIV-positive patients [1]. Apart from risk factors related to the HIV infection and its treatment,

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Received: 7 March 2012; revised: 4 June 2012; accepted: 22 June 2012.

DOI:10.1097/QAD.0b013e3283574e71

HIV-positive patients often have a higher prevalence of traditional risk factors for kidney disease, such as arterial hypertension, diabetes mellitus and smoking, than seen in the background population [2,3].

CKD has been reported to occur more often in HIV-positive patients coinfected with hepatitis C virus (HCV). HCV infection has been associated with different nephropathies, especially membranoproliferative glomerulonephritis in patients with mixed cryoglobulinemia [4,5]. In the EuroSIDA study, we have previously shown that HCV-seropositive patients had a 75% increased risk of CKD compared with HCV-seronegative patients [6], and a recent meta-analysis showed that, compared to HIV-monoinfected patients, HIV/HCV-coinfected patients had a nearly 50% increased risk of CKD [7]. However, in these and other published studies, the HCV diagnosis was based on a positive HCV antibody test only. The influence of HCV viral load and genotype on the risk of development of CKD in patients coinfected with HIV and HCV, therefore, remains to be determined.

In the developed world, chronic HCV infection is predominantly acquired through IDU. A number of renal disorders have been associated with use of illicit drugs (e.g. heroin and cocaine) [8]. In addition, IDU carries a high risk of invasive bacterial infections, which can lead to renal impairment. It is, therefore, likely that some of the increased renal morbidity and mortality seen in HCV-positive patients is due to some of these risk factors and not the HCV *per se*. Furthermore, in HCV patients with advanced liver disease, HCV could cause CKD indirectly as part of a hepatorenal syndrome [9].

In the EuroSIDA study, we are prospectively following a large cohort of HIV/HCV-coinfected patients, well characterized in terms of HCV-RNA and HCV genotype status. The aim of the present study was, therefore, to investigate the impact of HCV viremia and genotype on the risk of development of CKD in HIV/HCV-coinfected patients in the EuroSIDA study.

Patients and methods

The EuroSIDA study is a prospective, observational cohort of 16 594 HIV-1-infected patients followed in 103 centers across Europe, Israel and Argentina. The study has been described in detail previously [6]. In brief, patients were enrolled into eight cohorts from May 1994 onward and last follow-up was in spring 2011. At recruitment, in addition to demographic and clinical information, a complete ART history is obtained, together with the most recent CD4 cell count, plasma HIV-RNA measurements and hepatitis B and C status (anti-HCV antibodies, HCV-RNA and genotype). At each follow-up visit, details on all CD4 cell counts and plasma HIV-RNA values measured since the last follow-up visit are extracted, as are latest hepatitis B and C status and the dates of starting and stopping each ARV drug received and the use of drugs for prophylaxis against opportunistic infections. The dates of diagnosis of all AIDS-defining illnesses, non-AIDS-defining malignancies and other serious infections are also recorded.

The EuroSIDA plasma repository was set up in 1997 and collects plasma samples from all patients at 6-month intervals and stores them at -80°C. Patients with unknown hepatitis B surface antigen (HBsAg) or HCV serostatus and with stored plasma samples were identified in 2006 and anti-HCV immunoglobulin G and HBsAg in these samples were determined. Serum HCV-RNA was quantified in all anti-HCV-positive samples using the Versant HCV-RNA v3.0 assay (Bayer Diagnostics, Berkeley, California, USA), which has a lower limit of detection of 615 IU/ml.

Patients were included if they fulfilled the following inclusion criteria: a minimum of three serum creatinine measurements measured after 1 January 2004 (date from which serum creatinine has been routinely recorded in the EuroSIDA study), body weight measured within 12 months of each creatinine measurement, recorded date of birth and known HCV antibody status.

Study endpoints

Development of CKD was defined as either confirmed (at least two measurements at least 3 months apart) estimated glomerular filtration rate (eGFR) of 60 ml/min per 1.73 m^2 or less for patients with an eGFR more than 60 ml/min per 1.73 m^2 at baseline or confirmed 25% decline in GFR for patients with an eGFR of 60 ml/min per 1.73 m^2 or less at baseline. The eGFR was calculated using the Cockcroft–Gault equation [10]. Sensitivity analyses included using the Modification of Diet in Renal Disease (MDRD) [11] and Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equations [12] and using an endpoint defined as 25% decline to less than 60 ml/min per 1.73 m^2 or 25% decline in patients with baseline eGFR less than 60 ml/min per 1.73 m^2 [International Network for Strategic Initiatives in Global HIV Trials (INSIGHT); C. Wyatt *et al* , PLoS ONE, *in press*].

Statistical methods

Baseline in this analysis is defined as the first creatinine measurement taken after 1 January 2004 from which eGFR is calculated. Descriptive statistics such as χ^2-tests or nonparametric Kruskall–Wallis tests were used to compare patient characteristics at baseline. Progression to CKD was investigated using Poisson regression. Individuals were included in the analysis from baseline until the development of a confirmed CKD event, as previously described, or last eGFR measurement. In addition to HCV coinfection, other potential explanatory variables

included age, sex, race, region of Europe, AIDS at baseline or during follow-up, CD4 T-cell count and nadir, HBsAg status, HIV viral load, previous use of nephrotoxic drugs (including pentamidine, cidofovir, acyclovir, foscarnet and amphotericin), angiotensin-converting enzyme inhibitor use, hypertension, diabetes, baseline eGFR and cumulative exposure to ARV drugs previously found to be associated with increased risk of CKD (tenofovir, indinavir, atazanavir and lopinavir) [13]. Any explanatory variables with P value less than 0.1 in univariate analyses were subsequently included in multivariate analyses. Excluded variables were also tested in the multivariate model to see if their inclusion improved the model fit. Further analyses focusing on the role of HCV viremia and HCV genotype as explanatory variables along with many sensitivity analyses were performed by supplementing or restricting the main model. For categorical analysis HCV viremia was *a priori* categorized into resolved infection (<615 IU/ml), low viremia (615–500 000 IU/ml) and high viremia (>500 000 IU/ml).

Results

Baseline characteristics

Among 8235 patients included in the analysis, 2052 (24.9%) were anti-HCV-positive at baseline, of whom 983 (47.9%) were HCV-RNA-positive, 193 (9.4%) were HCV-RNA-negative and 876 (42.7%) had no HCV-RNA available at baseline. Patients with no HCV-RNA data available and no plasma available for HCV-RNA measurement were more likely to come from eastern Europe [adjusted odds ratio (aOR) 1.78, 95% confidence interval (CI) 1.38–2.30, $P < 0.0001$] and less likely to come from central Europe (aOR 0.24, 95% CI 0.16–0.36, $P < 0.0001$) than southern Europe and Argentina. They were more likely to have had a previous AIDS diagnosis (aOR 1.36, 95% CI 1.08–1.72, P=0.0097), undetectable HIV-RNA (aOR 1.57, 95% CI 1.26–1.98, $P < 0.0001$) and have unknown HBsAg status (aOR 3.59, 95% CI 2.03–6.36, $P < 0.0001$) than HBsAg positive.

Table 1 shows a breakdown of the baseline characteristics according to HCV serostatus. The anti-HCV-positive and anti-HCV-negative groups differed with respect to most variables. The anti-HCV-positive patients were slightly younger (39 vs. 42 years), more likely to being infected with HIV by IDU (71.5 vs. 2.4%), more likely to be current smokers (51.5 vs. 28.3%), had lower cART use (81.5 vs. 86.3%), had lower prevalence of hypertension (14.7 vs. 25.9%) and had higher eGFR (100.4 vs. 96.6 ml/min per 1.73 m^2) ($P < 0.0001$ for all comparisons).

Among anti-HCV-positive patients, there were few differences when comparing HCV-RNA-positive with HCV-RNA-negative patients (Table 1). Viremic patients were more likely to be IDU (74.4 vs. 64.3%), and had lower prevalence of HBsAg (5.3 vs. 14.0%) ($P < 0.0001$ for comparisons). There was no difference in the prevalence of diabetes between the two groups (3.7 vs. 5.2%, $P = 0.32$). In HCV-RNA-positive patients, the baseline $\log_{10}$-median HCV viral load was 5.74 IU/ml [interquartile range (IQR) 5.28–6.22], 468 (46.9%) had HCV-RNA between 615 and 500.000 IU/ml and 530 (53.1%) had viral load more than 500.000 IU/ml.

Factors associated with progression to chronic kidney disease

A total of 495 patients (6.0%) progressed to CKD during 36123 person-years of follow-up (PYFU), resulting in an overall crude incidence of CKD of 13.7 per 1000 PYFU (95% CI 12.5–14.9). One hundred twenty (24.2%) events occurred in anti-HCV-positive patients (incidence 14.5 per 1000 PYFU, 95% CI 11.9–17.1) with 81, seven and 32 events in the HCV-RNA-positive patients (18.7 per 1000 PYFU, 95% CI 14.7–22.7), HCV-RNA-negative patients (7.8 per 1000 PYFU, 95% CI 2.1–13.6) and HCV-RNA unknown groups (10.7 per 1000 PYFU, 95% CI 7.03–14.4), respectively. Three hundred and seventy-five (75.8%) events occurred in anti-HCV-negative patients (incidence 13.5 per 1000 PYFU, 95% CI 12.1–14.8).

The unadjusted and adjusted incidence rate ratios (IRRs) for the development of CKD for all included patients are shown in Fig. 1. In adjusted analysis, age (per 10 years older) and development of AIDS during follow-up were associated with higher incidence rate of CKD, whereas male sex and higher nadir $CD4^+$ cell count were associated with lower incidence of CKD. Use of tenofovir, atazanavir, indinavir and lopinavir (per year cumulative exposure) were all significantly associated with an increased incidence of CKD. Diabetes was associated with an increased incidence of CKD in univariate analysis (IRR 2.99, 95% CI 2.32–3.87, $P < 0.0001$), but was excluded from multivariate analysis due to high colinearity with hypertension. Lower current $CD4^+$ cell count and elevated HIV-RNA levels were both associated with an increased incidence of CKD in the univariate analysis, but not after adjustment.

In univariate analyses, HCV serostatus did not influence the incidence of CKD (IRR 1.07, 95% CI 0.87–1.31, $P = 0.54$). After adjustment, anti-HCV-positive patients had a two-fold increased incidence of CKD compared with anti-HCV-negative patients (IRR 1.85, 95% CI 1.49–2.30, $P < 0.0001$). The main factors responsible for the change in IRR in the multivariate analysis were the younger age and the higher baseline eGFR of the anti-HCV-positive patients compared with the anti-HCV-negative patients. Adjustment for injection drug use as HIV transmission risk group did not change the results, and was not included in the final model due to colinearity between this variable and HCV status. HBsAg serostatus

Table 1. Baseline characteristics according to hepatitis C virus serostatus.

	All ($N = 8235$)	Anti-HCV-positive ($n = 2052$) (24.9%)	Anti-HCV-negative ($n = 6183$) (75.1%)	P value*	HCV-RNA-positive ($n = 983$) (83.6%	HCV-RNA-negative ($n = 193$) (16.4%)	P value**
Age, median (IQR) years	41 (35–48)	39 (33–44)	42 (36–50)	<0.0001	41 (36–45)	41 (38–45)	0.17
Sex: male (%)	73.9	67.8	75.9	<0.0001	68.2	64.8	0.36
Race (%)							
White	88.9	93.3	87.4	<0.0001	91.3	88.5	0.51
Asian	1.4	0.5	1.7		0.6	0.5	
Black	5.7	1.1	7.3		0.7	1.6	
Unknown	4.0	5.1	3.6		7.4	9.4	
Region (%)							
South/Argentina	25.8	30.8	24.1	<0.0001	34.6	28.0	0.040
Central Europe	26.7	18.4	29.5		25.9	28.5	
North Europe	23.6	12.3	27.4		13.3	20.2	
East Europe	23.9	38.6	19.0		26.1	23.3	
Risk group (%)							
MSM	41.6	7.5	53.0	<0.0001	6.9	17.1	0.0001
IDU	19.7	71.5	2.4		74.4	64.3	
Heterosexual	30.8	13.6	36.5		11.3	13.0	
Other	8.0	7.3	8.2		7.4	5.7	
Prior AIDS (%)	29.7	30.6	29.5	0.34	27.7	36.3	0.016
HBsAg (%)							
Positive	6.0	6.6	5.8	<0.0001	5.3	14.0	<0.0001
Negative	90.0	86.9	91.1		90.7	82.4	
Unknown	4.0	6.5	3.1		4.0	3.6	
cART (%)	85.1	81.5	86.3	<0.0001	90.1	90.2	0.84
HIV-RNA <500 copies/ml (%)	71.3	69.9	71.7	0.15	74.8	71.7	0.37
CD4 cell count, median (IQR) cells/μl	439 (294–625.5)	400 (257–584)	450 (310–640)	<0.0001	418 (277–595)	435 (304–640)	0.32
CD4 nadir, median (IQR) cells/μl	141 (51–237)	130.5 (50–220)	146 (51–242)	0.0002	122 (41–209)	98 (26–176)	0.028
ACE inhibitor use (%)	4.1	2.2	4.7	<0.0001	2.3	4.2	0.15
Nephrotoxic drugs[a] (%)	12.0	10.5	12.5	0.017	13.4	13.0	0.86
Prior CVD risk (%)							
Stroke	0.9	0.4	1.1	0.0036	0.5	0	0.32
Myocardial infarction	1.4	0.8	1.6	0.013	0.6	2.1	0.043
Angioplasty	1.1	0.5	1.3	0.0036	0.3	0.5	0.64
Coronary bypass	0.5	0.2	0.6	0.013	0.2	0.5	0.43
Diabetes	4.5	3.7	4.8	0.028	3.7	5.2	0.32
Hypertension	23.1	14.7	25.9	<0.0001	16.1	18.1	0.48
Smoking (%)							
Never	31.3	17.0	36.0	<0.0001	16.1	21.8	0.18
Current	34.1	51.5	28.3		56.2	54.4	
Former	4.2	4.4	4.2		5.2	5.2	
Unknown	30.4	27.1	31.5		22.6	17.6	
eGFR (ml/min per 1.73 m^2)	97.6 (83.8–113.0)	100.4 (86.5–115.6)	96.6 (82.9–112.0)	<0.0001	99.5 (86.3–115.1)	101.7 (86.5–114.3)	0.80
Cumulative tenofovir use, median (IQR) months	0 (0–1)	0 (0–0)	0 (0–1)	0.090	0 (0–2)	0 (0–0)	0.024

ACE, angiotensin-converting enzyme; cART, combination antiretroviral treatment; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IQR, interquartile range.

[a]Pentamidine, cidofovir, acyclovir, foscarnet or amphotericin.

*Compares anti-HCV-positive with anti-HCV-negative patients.

**Compares HCV-RNA-positive with HCV-RNA-negative patients.

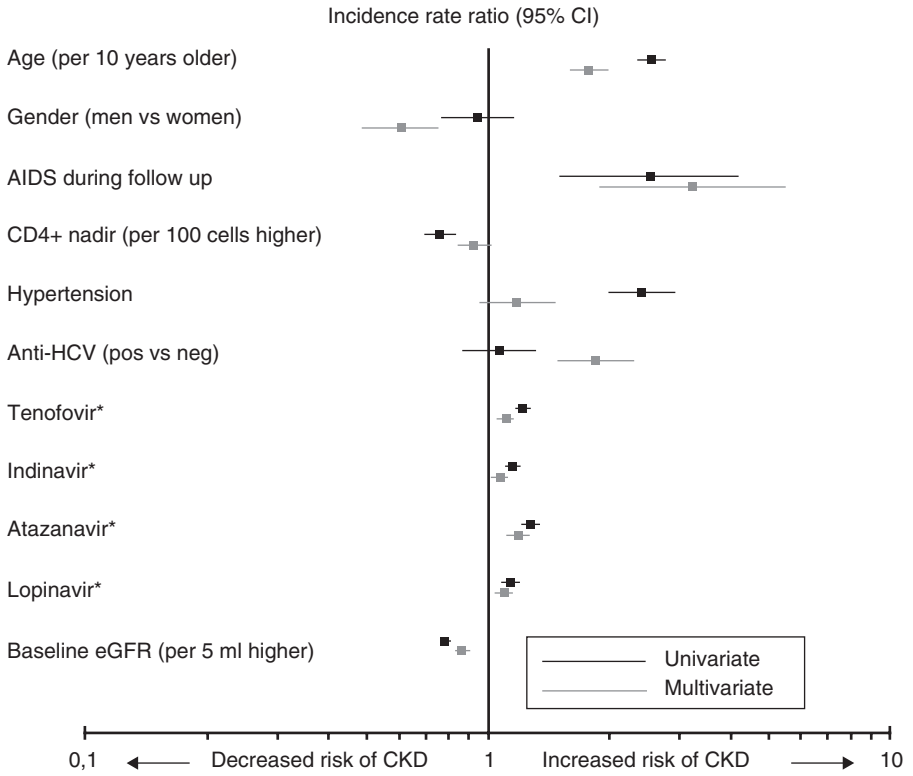

Fig. 1. Incidence rate ratio (95% confidence interval) of developing chronic kidney disease in univariate and multivariate analysis. Multivariate analyses adjusted for age*, sex, region of Europe, AIDS at baseline, AIDS during follow-up*, CD4 T-cell count*, CD4 T-cell nadir, HIV-RNA*, use of nephrotoxic drugs*, ACE inhibitor use*, hypertension*, hepatitis C virus (HCV) status*, baseline estimated glomerular filtration rate (eGFR), hepatitis B surface antigen (HBsAg) status* and exposure to tenofovir*, indinavir*, lopinavir* and atazanavir* (per year cumulative exposure). CI, confidence interval; CKD, chronic kidney disease. *Time-updated variable.

(positive vs. negative) did not influence the incidence of CKD in either univariate or multivariate analysis.

Hepatitis C virus viremia and genotype and the incidence of chronic kidney disease

In univariate analysis, there was no difference in the incidence of CKD when comparing anti-HCV-negative patients with anti-HCV-positive patients with resolved infection ($P=0.51$), unknown viremia ($P=0.15$) or HCV-RNA between 615 and 500.000 IU/ml ($P=0.41$). Patients with HCV-RNA more than 500.000 IU/ml had a higher incidence of CKD compared with anti-HCV-negative patients, which approached statistical significance (IRR 1.35, 95% CI 1.00–1.83, $P=0.053$) (Fig. 2). After adjustment, those with resolved HCV infection had a similar incidence of CKD as those with anti-HCV-negative patients (IRR 1.17, 95% CI 0.65–2.09, $P=0.60$), whereas patients with HCV-RNA between 615 and 500.000 IU/ml had an elevated incidence (IRR 1.88, 95% CI 1.31–2.71, $P=0.0006$), with the highest incidence seen in those with HCV-RNA more than 500 000 IU/ml (IRR 2.10, 95% CI 1.54–2.87, $P<0.0001$). The difference in incidence of CKD for high vs. low viremia was not statistically significant (IRR 1.18, 95% CI 0.75–1.85, $P=0.49$). Fitting HCV-RNA as a continuous variable on the $\log_{10}$ scale, a 1-log increase in HCV-RNA was associated with 9% increased incidence of CKD, although not statistically significant (IRR 1.09, 95% CI 0.95–1.24, $P=0.21$). For the group with unknown viremia, the incidence of CKD was comparable to the incidence for viremic patients (IRR 1.91, 95% CI 1.26–2.87, $P<0.0021$). The incidence of CKD did not vary by HCV genotype (IRR 1.06, 95% CI 0.68–1.65, $P=0.81$ for comparing HCV genotype 1 with HCV genotype 2–4).

A sensitivity analysis that included IDUs only, including 1618 individuals and 85 CKD events at an incidence of 13.0 per 1000 PYFU (IQR 10.2–15.7), showed similar results, although the statistical power was reduced. With anti-HCV-positive/HCV-RNA-negative patients as reference, the adjusted IRR for CKD was 1.22 (95% CI 0.49–3.03, $P=0.67$) and 1.99 (95% CI 0.86–4.61, $P=0.11$) for patients with low (615–500.000 IU/ml) and high HCV viremia (>500.000 IU/ml), respectively.

The results of the different sensitivity analyses, using other formulae for eGFR, are shown in Fig. 3. Using the MDRD and the CKD-EPI formulae produced similar results as for the Cockcroft–Gault equation. Repeating

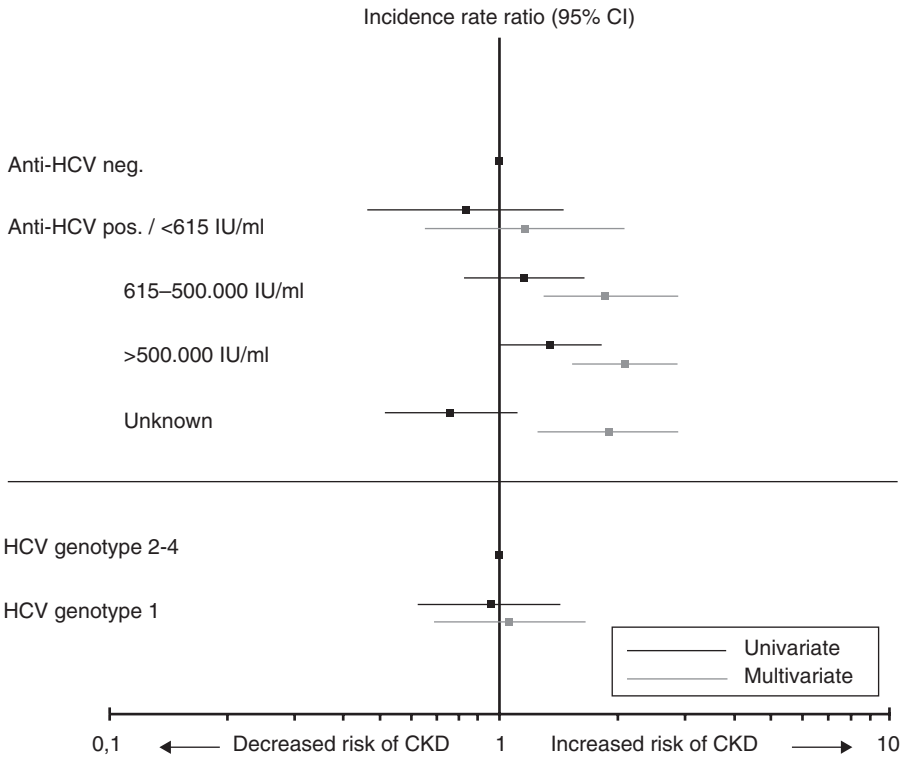

Fig. 2. Incidence rate ratio (95% confidence interval) of developing chronic kidney disease according to hepatitis C virus viral load strata and genotype. Multivariate analyses adjusted for age*, sex, region of Europe, AIDS at baseline, AIDS during follow-up*, CD4 T-cell count*, CD4 T-cell nadir, HIV-RNA*, use of nephrotoxic drugs*, ACE inhibitor use*, hypertension*, baseline estimated glomerular filtration rate (eGFR), hepatitis B surface antigen (HBsAg) status* and exposure to tenofovir*, indinavir*, lopinavir* and atazanavir* (per year cumulative exposure). CI, confidence interval; CKD, chronic kidney disease. *Time-updated variable.

the Cockcroft–Gault analysis with a definition of CKD with greater specificity (INSIGHT definition; 25% decline to <60 ml/min per 1.73 m^2 or 25% decline in participants with baseline eGFR <60 ml/min per 1.73 m^2) strengthened the association between HCV viremia and the incidence of CKD (IRR 2.72, 95% CI 1.82–4.06, $P < 0.0001$) and (IRR 2.77, 95% CI 1.93–3.98, $P < 0.0001$) for low and high viremia, respectively. Comparing high vs. low viremia was not statistically significant ($P = 0.94$)

To investigate whether the increased risk of CKD in patients with chronic HCV infection could be due to advanced liver disease, we analyzed the IRR for progression to CKD according to plasma levels of the liver fibrosis marker hyaluronic acid in 682 (69.4%) anti-HCV-positive patients who had this test performed in their first available plasma sample after they were known to be anti-HCV-positive. Fitting hyaluronic acid as a continuous variable on the $\log_{10}$ scale, a 1-log increase in hyaluronic acid was associated with an increased risk of CKD in univariate analysis (IRR 2.64, 95% CI 1.48–4.69, $P = 0.0010$); however, after adjustment for all other variables in Fig. 1, this was no longer statistically significant (IRR 1.74, 95% CI 0.91–3.34, $P = 0.093$).

Discussion

The present study is among the first to investigate the association between HCV-RNA viral load, genotype and the incidence of CKD in a large cohort of HIV/HCV-coinfected patients. The incidence of CKD was similar between patients with resolved HCV infection and in anti-HCV-negative patients, whereas patients with chronic HCV infection had a two-fold increased incidence of CKD compared with anti-HCV-negative patients. There was no difference in incidence of CKD when comparing patients with high vs. low HCV viremia. Sensitivity analyses, using the MDRD and the CKD-EPI formulae, gave similar results. To overcome a limitation related to our definition of CKD, which means that patients with a minimal confirmed decrease in eGFR, for example, from 61 to 59 ml/min per 1.73 m^2, would be classified as having CKD; we also used a stricter definition requiring 25% decline to less than 60 ml/min

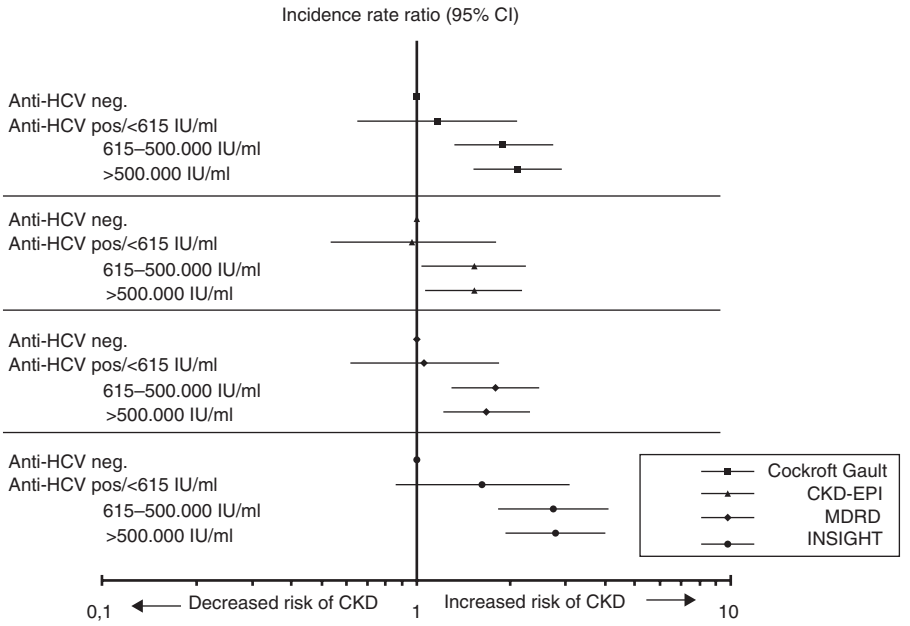

Fig. 3. Sensitivity analyses of incidence rate ratio (95% confidence interval) of developing chronic kidney disease according to hepatitis C virus viral load strata. Multivariate analyses adjusted for age*, sex, region of Europe, AIDS at baseline, AIDS during follow-up*, CD4 T-cell count*, CD4 T-cell nadir, HIV-RNA*, use of nephrotoxic drugs*, ACE inhibitor use*, hypertension*, baseline estimated glomerular filtration rate (eGFR), hepatitis B surface antigen (HBsAg)* and exposure to tenofovir*, indinavir*, lopinavir* and atazanavir* (per year cumulative exposure). CI, confidence interval; CKD, chronic kidney disease. *Time-updated variable.

per 1.73 m^2 or 25% decline in participants with baseline eGFR less than 60 ml/min per 1.73 m^2, which only strengthened the association between HCV viremia and CKD. There were no differences according to HCV genotype. Taken together, these results indicate that the HCV itself is a significant risk factor for development of CKD in HIV-coinfected patients.

Our results are consistent with findings from a study of HIV/HCV-coinfected patients enrolled in the standard therapy arms of the Strategic Management of Antiretroviral Therapy and Evaluation of Subcutaneous Proleukin in a Randomized International trials (C. Wyatt *et al*, PLoS ONE, *in press*). A recent retrospective study of HCV-monoinfected patients found a 2.5-fold increased odds of CKD among patients with baseline HCV-RNA more than 700 000 copies/ml compared with patients with HCV-RNA less than 700 000 IU/ml, but the study was not powered to compare patients with chronic vs. resolved HCV infection [14]. In contrast, a large cohort study by Butt *et al.* [15] of HIV-negative American male veterans showed no difference in time to development of CKD when comparing individuals with resolved ($n = 1793$) and chronic HCV infection ($n = 11\,822$). This study differs from ours in several important ways. In the American study, patients were 12 years older and had a much higher prevalence of traditional risk factors for CKD, such as hypertension and diabetes, which could have diminished the relative importance of HCV.

The present study does not allow for conclusions on how HCV increases the risk of CKD. Many HCV-related nephropathies have been described; the leading cause of HCV-related kidney disease is membranoproliferative glomerulonephritis due to mixed cryoglobulinemia with deposition of HCV containing immune complexes in the glomeruli [5,16]. Reported prevalence rates of cryoglobulinemia in HCV infection vary widely from 36% to 90%, which can partly be explained by methodological differences, but the prevalence has also been shown to increase with longer duration of HCV infection and severity of liver fibrosis [4]. However, the prevalence of symptoms related to cryoglobulinemia, such as vasculitis, arthralgia and glomerulonephritis, is much lower than that of cryoglobulinemia. Most studies have found a similar prevalence of cryoglobulinemia in HCV patients coinfected with HIV [17–19]. In our study, we were not able to characterize the type of CKD, as data on kidney biopsies, cryoglobulinemia and proteinuria were not available.

Further, we cannot rule out that some of the increased risk of CKD in patients with chronic HCV infection could be due to the consequences of IDU. However, our results were similar, although the statistical power

considerably lower, after exclusion of individuals from HIV transmission risk groups other than IDU. We were not able to evaluate the effect of active IDU in depth at present, as a standardized data collection on these aspects has only recently been implemented.

There was a trend toward increased risk of CKD in patients with elevated levels of the liver fibrosis marker hyaluronic acid, but this did not reach statistical significance after adjustment. However, as only 69% of all patients had been tested for hyaluronic acid and only at one time point, we cannot rule out that hepatic disease is an important risk factor for CKD in this population; for example, in a retrospective study of 650 HCV patients with cirrhosis, the long-term risk of CKD was 2.7-fold higher among those who did not clear HCV-RNA after interferon treatment [20].

In EuroSIDA, we have previously reported the association between specific ARVs (tenofovir, atazanavir, indinavir and perhaps also lopinavir) and increased risk of CKD, and that the ARV-related nephrotoxicity seems to be reversible [13]. Current guidelines from the European Clinical AIDS Society recommend that HIV patients initiating ART that includes one of these drugs should be monitored more frequently for development of CKD, particularly if they also have other risk factors for CKD [21].

In conclusion, in the EuroSIDA observational HIV cohort, we have shown that chronic, but not resolved HCV infection, was associated with an increased risk of CKD compared with HIV-monoinfected patients. The exact nature of this association could not be determined in our study. If our results are confirmed by others, future larger studies are warranted to explore the reversibility of CKD in patients undergoing anti-HCV therapy, and investigate the interaction between HIV/HCV coinfection and certain ARV drugs known to be nephrotoxic.

Acknowledgements

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Conflicts of interest

Primary support for EuroSIDA is provided by the European Commission BIOMED 1 (CT94-1637), BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773), the 6th Framework (LSHP-CT-2006-018632) and the 7th Framework (FP7/2007-2013, EuroCoord 260694) programs. Current support also includes unrestricted grants by Gilead, Pfizer and Merck and Co. The participation of centers from Switzerland was supported by The Swiss National Science Foundation (Grant 108787).

There are no conflicts of interest.

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