Influence of hepatitis C virus co-infection and hepatitis C virus treatment on risk of chronic kidney disease in HIV-positive persons

AIDS

Influence of Hepatitis C (HCV) Co-Infection and HCV Treatment on Risk of Chronic Kidney Disease in HIV Positive Persons

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Abstract:	Background: Hepatitis C virus (HCV) infection has been associated with increased risk of chronic kidney disease (CKD). We investigated the impact of HCV cure on CKD in HIV-positive persons in the EuroSIDA study. Methods: HIV-positive persons with known HCV status and > 3 serum creatinine measurements after 1/1/2004 were compared based on time-updated HCV-RNA and HCV treatment: Anti-HCV negative, spontaneously cleared HCV, Chronic untreated HCV, successfully treated HCV and HCV-RNA positive after HCV treatment. Poisson regression compared incidence rates of CKD (confirmed [>3 months apart] eGFR < 60 ml/min/1.73m 2) between HCV strata. Results: 14754 persons were included; at baseline 9273 (62.9%) were HCV-Ab negative, 696 (4.7%) spontaneous clearers, 3021 (20.5%) chronically infected, 922 (6.2%) successfully treated and 842 5.7%) HCV-RNA positive after treatment. During 115335 person-years of follow-up (PYFU), 1128 (7.6%) developed CKD; crude incidence 9.8/1000 PYFU (95% CI 9.2–10.4). After adjustment, persons Anti-HCV negative (adjusted incidence rate ratio [aIRR] 0.59; 95% CI 0.46-0.75) and spontaneous clearers (aIRR 0.67; 95% CI 0.47-0.97) had significantly lower rates of CKD compared to those cured while persons chronically infected (aIRR 0.85; 95% CI 0.65-1.12) and HCV-RNA positive after treatment (aIRR 0.71; 95% CI 0.49-1.04) had similar rates. Analysis in those without F3/F4 liver fibrosis and using a more rigorous definition of CKD showed similar results. Conclusions: This large study found no evidence that successful HCV treatment reduced CKD incidence. Confounding by indication, where those with highest risk of CKD were prioritized for HCV treatment in the DAA era, may contribute to these findings.

Influence of Hepatitis C (HCV) Co-Infection and HCV Treatment on Risk of Chronic Kidney Disease in HIV Positive Persons

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Abstract

Background: Hepatitis C virus (HCV) infection has been associated with increased risk of chronic kidney disease (CKD). We investigated the impact of HCV cure on CKD in HIV-positive persons in the EuroSIDA study.

Methods: HIV-positive persons with known HCV status and ≥3 serum creatinine measurements after 1/1/2004 were compared based on time-updated HCV-RNA and HCV treatment: Anti-HCV negative, spontaneously cleared HCV, Chronic untreated HCV, successfully treated HCV and HCV-RNA positive after HCV treatment. Poisson regression compared incidence rates of CKD (confirmed [>3 months apart] eGFR < 60 ml/min/1.73m^2) between HCV strata.

Results: 14754 persons were included; at baseline 9273 (62.9%) were HCV-Ab negative, 696 (4.7%) spontaneous clearers, 3021 (20.5%) chronically infected, 922 (6.2%) successfully treated and 842 5.7%) HCV-RNA positive after treatment. During 115335 person-years of follow-up (PYFU), 1128 (7.6%) developed CKD; crude incidence 9.8/1000 PYFU (95% CI 9.2–10.4). After adjustment, persons Anti-HCV negative (adjusted incidence rate ratio [aIRR] 0.59; 95% CI 0.46-0.75) and spontaneous clearers (aIRR 0.67; 95% CI 0.47-0.97) had significantly lower rates of CKD compared to those cured while persons chronically infected (aIRR 0.85; 95% CI 0.65-1.12) and HCV-RNA positive after treatment (aIRR 0.71; 95% CI 0.49-1.04) had similar rates. Analysis in those without F3/F4 liver fibrosis using a more rigorous definition of CKD showed similar results.

Conclusions: This large study found no evidence that successful HCV treatment reduced CKD incidence. Confounding by indication, where those with highest risk of CKD were prioritized for HCV treatment in the DAA era, may contribute to these findings.

Introduction

Hepatitis C virus (HCV) coinfection has been implicated in a range of extra-hepatic diseases in HIV-positive persons including kidney disease [1-6]. . Some studies found those with chronic HCV infection had more chronic kidney disease (CKD) compared with those with spontaneously cleared infection [1, 3] , while Butt et al found no difference comparing those with chronic and cleared infection [7]. Many of the earlier studies were limited by lack of data on HCV-RNA and were therefore unable to distinguish between chronic untreated or spontaneously cleared HCV infection. The impact of HCV-related systemic inflammation and risk of CKD remains unclear, as highlighted in a recent review [8].

The introduction of direct acting antivirals (DAAs) for the treatment of HCV has had a major impact on HCV treatment [9] with cure rates in excess of 90% in persons coinfected with both HIV and HCV [10]. Case reports have shown that achievement of a sustained virological response (SVR) resulted in improvement in kidney function in persons with HCV-related glomerular nephritis [11].Cohort studies, including 100-350 persons with SVR and with no known underlying renal pathology, have been unable to document an improvement in kidney function in those with SVR compared with those treated for HCV without SVR [12-14]. One further study reported a protective effect of SVR on CKD [15] which did not reach statistical significance and did not adjust for baseline renal function. Changes in renal function in these studies was measured in a variety of ways, and while slopes or rate of change in estimated glomerular filtration rate (eGFR) might be useful to study short term changes in renal function, a more rigorous definition of renal decline requiring confirmed low values over a period of 3 months, such as CKD [2], has greater clinical relevance given its association with other clinical events, including cardiovascular disease [16].

Given the lack of consensus from previous studies, methodological issues and the limited power and/or follow-up, we sought to investigate the incidence of CKD in a large pan-European multi-cohort study according to HCV status in HIV-coinfected persons across 5 groups: Anti-HCV negative, spontaneous HCV-RNA clearers, chronic untreated HCV infection, cured HCV and HCV-RNA positive following HCV treatment.

Methods

The EuroSIDA study

Persons were included from the EuroSIDA study, a large prospective observational cohort of almost 23000 HIV-1 positive patients followed in 100 hospitals in 35 European countries plus Israel and Argentina. Individuals were enrolled into ten cohorts from 1994 onward. In cohort ten all HIV positive patients were also required to be positive for anti-HCV antibodies (HCV-RNA positive, negative or unknown status). At recruitment, in addition to demographic and clinical data, a complete ART history was obtained together with the most recent CD4 cell counts and HIV-RNA measurements, as well as all HCV tests, HCV-RNA, HCV genotype, hepatitis B surface antigen (HBsAg) and HBV-DNA. Data is collected prospectively at clinical sites and sent to the coordinating centre at yearly intervals. At each follow-up visit, all CD4 cell counts, HIV-RNA, HCV tests, HCV-RNA, genotype, and HBsAg results measured since last follow-up are collected, together with start and stop dates for antiretroviral drugs and HCV and HBV drugs. Detailed information about data collected in EuroSIDA can be found at http://www.chip.dk/Ongoing-Studies/EuroSIDA/About.

Methods and definitions

CKD was defined as a confirmed (>3 months apart) eGFR < 60/ml/min/1.73m^2 for those with first eGFR > 60/ml/min/1.73m^2 and a confirmed (>3 months apart) 25% decline in eGFR for those with baseline eGFR $\leq$60/ml/min/1.73m^2. eGFRs were calculated using the CKD-EPI formula [17]. All persons with known HCV serostatus and prospective follow-up after 1 January 2004 (start of standardised collection of serum creatinine) were eligible for inclusion. Persons with <3 eGFRs during prospective follow-up were excluded, as were persons with less than 3 months follow-up. Baseline was defined as the first prospective visit in EuroSIDA after 1/1/2004 at which both eGFR and HCV serostatus were measured, and where HCV-RNA was known for those Anti-HCV positive. Persons aged < 16 at baseline or without a CD4 count and HIV viral load in the 12 months before or 1 month after baseline were excluded.

Based on time-updated HCV antibody tests, HCV-RNA and HCV treatment, we defined 5 HCV groups

1. Anti-HCV negative
2. HCV antibody positive, HCV-RNA negative, untreated (spontaneous clearers)
3. HCV antibody positive, HCV-RNA positive, untreated (chronic infections)
4. HCV antibody positive, HCV-RNA negative, treated (successfully treated with any HCV therapy; cured)

5. HCV antibody positive, HCV-RNA positive, treated (treated, HCV-RNA positive)

All groups Anti-HCV positive were defined on the basis of a single HCV-RNA measurement; for example, persons were classified as spontaneous clearers based on the latest value of HCV-RNA. Those HCV-RNA positive after treatment included persons who did not achieve SVR, persons without an end of treatment response, persons who were HCV-RNA positive having started treatment more recently and those reinfected with HCV. Persons were followed until their last visit (median June 2018), date of death, or CKD, whichever occurred first. Person years of follow-up (PYFU) and CKD events accrued according to current HCV strata using the last observation carried forward and persons could contribute PYFU to multiple groups.

In those that developed CKD, we performed an exploratory analysis looking at reversal of CKD. This was defined as a confirmed (> 3 months apart) increase in eGFR to > 60/ml/min/1.73m^2 among persons with at least 2 further eGFRs and 3 months follow-up after CKD. Baseline for this analysis was date of developing CKD, and individuals were followed to the first of reversal of CKD or last eGFR.

Statistical Analysis

Characteristics of individuals were compared across strata using chi-squared statistics for categorical variables and the Kruskall-Wallis test for continuous variables. Incidence rates of CKD per 1000 person-years of follow-up (PYFU) were calculated within HCV groups, and Poisson regression was used to compare these rates with those cured as the reference group. Different models were investigated; the first adjusted only for the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study CKD risk score [18], without including the component due to HCV coinfection. Liver fibrosis stage (as previously described; [19]; this was included as a baseline measurement as it may lie on the causal pathway between HCV status and CKD) and the HCV strata defined above were also included in this model. As the D:A:D CKD risk score does not include all the variables which differed between the HCV strata, we also investigated a more extensive model adjusting for many more potential confounding variables. This second model adjusted for a greater number of potential confounding factors, all fixed at baseline (gender, HIV exposure group, region of Europe Europe (North, Central West, South, Central East, East and Argentina [20]), eGFR, HIV viral load, prior AIDS, cardiovascular disease, non-AIDS defining malignancies (NADM), end stage liver disease (ESLD; ascites, hepatorenal syndrome, grade III/IV hepatic encephalopathy, unspecified liver decompensation, oesophageal variceal bleeding, spontaneous bacterial peritonitis, liver transplantation and hepatocellular carcinoma). Further information about these events is available at https://www.chip.dk/Studies/EuroSIDA/Study-documents). We also adjusted for smoking status (never smoked, current smoker, past smoker, unknown smoking status), hypertension, body mass index (BMI), use of nephrotoxic ARVs (tenofovir, atazanavir [unboosted and/or ritonavir boosted], indinavir, and lopinavir), use of nephrotoxic drugs (foscarnet, acyclovir, pentamidine, cidofovir, amphotericin B), CD4, nadir CD4, age, liver fibrosis and baseline date. A third model adjusted for baseline liver fibrosis and the components of the D:A:D CKD risk score (including use of nephrotoxic ARVs and HCV status as defined in this study) at baseline as separate variables rather than a composite score. The model was additionally adjusted for starting integrase inhibitors, shown to increase serum creatinine levels [21], as a time updated variable. As results were consistent across models, our results focus on model 3 which had the lowest Akaike Information Criterion.

We performed a wide range of sensitivity analyses to investigate the robustness of our results to different assumptions. We performed a sensitivity analysis where the last HCV-RNA measurement was carried forward for a maximum of 12 months. This reduces the bias from HCV-RNA measurements measured many years previously being used to stratify persons into HCV strata. We also excluded persons with stage F3/F4 liver fibrosis at baseline, as well as PYFU and CKD events

occurring after the development of F3/F4 liver fibrosis in the subgroup of persons at high risk for CKD using the D:A:D CKD risk score[18], and an analysis limited to after 2014, when DAAs became more widely available for persons included in the EuroSIDA study [22]. We also explored a more rigorous definition of CKD as a confirmed 25% decline to <60/ml/min/1.73m^2 [1]. We repeated our analyses separately among those treated and cured or HCV-RNA positive after treatment in those not exposed, or only exposed, to DAA-based regimens.

All analyses were performed in SAS version 9.4 (Statistical Analysis Software, Cary NC, USA).

Results

Of 22826 persons enrolled in EuroSIDA, 6806 were excluded due to unknown HCV status, insufficient follow-up or with CKD before baseline. An additional 1266 persons were excluded with unknown HCV-RNA status for those who were anti-HCV positive, or with missing baseline CD4 counts and viral load. Compared to the 14754 included, the 1266 excluded were less likely to be MSM, were less likely to be from Central, or West Europe and more likely to be from Central East, Eastern Europe or Argentina compared to southern Europe. They were also less likely to have suppressed HIV viral load and more likely to have a prior AIDS diagnosis (all $p<0.05$).

Table 1 shows the characteristics of the 14754 included persons, stratified by baseline HCV strata. The 5 HCV strata were quite heterogenous and there were many significant differences across the groups (see footnote to Table 1). As would be expected, the proportion of injecting drug uses (IDUs) was lowest in those Anti-HCV negative, the proportion with prior ESLD (only 3 persons had a prior diagnosis of hepatorenal syndrome) was highest in those HCV-RNA positive after treatment and the burden from F3/F4 liver fibrosis was highest in both those cured and HCV-RNA positive after treatment, as was the proportion who had received tenofovir disoproxil fumarate (TDF) at baseline. The median age was 43 years (interquartile range [IQR] 37 - 51), baseline CD4 cell count was 470/mm^3 (IQR 318–669) and CD4 nadir 174/mm^3 (IQR 70–281). 1764 persons had been previously treated for HCV; the majority of these (1467; 83.2%) had been treated with interferon plus ribavirin. At baseline, 181 had received a DAA plus interferon, and 275 had received DAAs without interferon.

The analysis included 280,022 eGFRs with a median of 16 (IQR 8–28) per person and 2.4 (IQR 1.9–3.0) per year of follow-up. The number of measures per person per year were similar across the 5 HCV strata, ranging from 2.2/year (IQR 1.7–3.0) in spontaneous clearers to 2.4/year in those Anti-HCVnegative, those cured and those HCV-RNA positive after treatment. The median eGFR at baseline was 99 ml/min/1.73m^2 (IQR 85- 110). 4420 (30.0%) were at low risk of CKD using the D:A:D risk score, 5089 (34.5%) were at medium risk and 5243 (35.5%) were at high risk, with significant differences between HCV strata. At baseline, 2842 of those Anti-HCV negative were at high risk (30.6%), increasing to 545 of those cured (59.1%) and 425 in those HCV-RNA positive after treatment (50.5%).

<u>The incidence of CKD in HCV strata</u>

During 115,335 PYFU; a median 7.0 (IQR 3.7–12.4) per person, 1130 (7.7%) developed CKD; the crude incidence rate per 1,000 person-years of follow-up was 9.8 (95% confidence interval [CI] 9.2–10.4). Table 2 shows the crude incidence rate in each of the HCV strata. The incidence rate was

lowest in those HCV-RNA positive following treatment; incidence rate 7.7/1000 PYFU; 95% CI 5.2–10.1) and highest in those cured; 12.9/1000 PYFU (95% CI 10.4–15.3). Figure 1 shows the univariate and multivariate incidence rate ratios of CKD compared to those cured. After adjustment (model 3, adjusting separately for the components of the D:A:D CKD risk score, liver fibrosis stage at baseline and use of integrase inhibitors those Anti-HCV negative (adjusted incidence rate ratio [aIRR] 0.50; 95% CI 0.39–0.63) and spontaneous clearers (aIRR 0.67; 95% CI 0.47-0.97) had significantly lower rates of CKD compared to those cured. Those chronically infected (aIRR 0.85; 95% CI 0.65-1.12) and HCV-RNA positive after treatment (aIRR 0.71; 95% CI 0.49-1.04) had non-significant reduced rates of CKD compared to those cured.

The proportion of follow-up time with eGFR > 90 ml/min/1.73m^2 was 62.5%, and was highest in those with chronic infections (69.2%) and lowest in those cured (55.0%). Of 1128 who developed CKD, 926 (82.1%) had at least 2 further eGFRs and 3 months follow-up. Of these 926, 442 (47.7%) had a reversal of CKD during subsequent follow-up. By 12 months after CKD, 17.2% were estimated to have reversed CKD (95% CI 14.7–19.7) from Kaplan-Meier estimates, with no differences between the HCV strata at development of CKD (p=0.56). The proportion who reversed CKD was lowest overall for those cured (23/72, 31.9%) and highest for those chronically infected (53/102, 52.0%), but this was not statistically significant (p=0.083). The median eGFR at CKD was 53.4 (IQR 47.2–57.0 ml/min/1.73m^2) and was lowest in those chronically infected (median 50.4, IQR 44.2–56.3 ml/min/1.73m^2), and highest in those anti-HCV negative (median 53.6, IQR 48.2–57.0 ml/min/1.73m^2).

Sensitivity analyses

The results from a wide range of sensitivity analyses showed similar results. Of note, an analysis excluding those with F3/F4 or unknown liver fibrosis at baseline included 442 events during 52085 PYFU (incidence of CKD 8.5/1000 PYFU; 95% CI 7.7–9.3) and showed similar results; albeit with wider confidence intervals. In this analysis, those anti-HCV negative had significantly reduced rates of CKD (aIRR 0.65; 95% CI 0.47–0.89) compared to those cured, with no significant differences between other groups (left hand side; Figure 2).

Our results were also consistent when we investigated separately HCV treatments including interferon or DAAs in those treated and cured or HCV-RNA positive after treatment, with limited power in the latter analysis. There were 1068 events during 111,228 PYFU when DAA treatments were excluded from those cured or HCV-RNA positive after treatment with an overall incidence rate of 9.6 (9.0–10.3), and the results are shown in the middle panel of Figure 2. Similarly, when only

including DAA treatments in those cured or HCV-RNA positive after treatment, there were 1036 events during 105,291 PYFU, and the results are shown on the right hand side of figure 2. In this analysis, those Anti-HCV negative had significantly lower rates of CKD and those with spontaneous clearance had marginally lower rates of CKD compared to those cured.

Having a more stringent definition for CKD of a confirmed 25% decline in eGFR to <60 ml/min/1.73m^2 resulted in a lower incidence of CKD (1001 events during 116369 PYFU, rate 8.6/1000 PYFU; 95% CI 8.1–9.1), but also showed a lower incidence of CKD in those anti-HCV negative), consistent with our main findings.

Characteristics of HCV treated persons at CKD or last visit

Our final analysis focused further on those treated for HCV. Characteristics of persons at CKD or last visit for those not developing CKD are shown in Table 3. Of note, there was a much higher proportion of persons with ESLD in those cured who developed CKD, likely reflecting targeted treatment to those with most advanced liver disease when DAAs first became available. As would be expected, those cured had a much higher proportion of people who had received DAA treatment compared to those HCV-RNA positive after treatment, regardless of whether they developed CKD or not.

Discussion

This large study of almost 15,000 individuals with a median follow-up of approaching 7 years and with known anti-HCV and HCV-RNA status has found no reduction in CKD among those with cured HCV infection following treatment for HCV. To date, this is the largest study focused on CKD in HIV and HCV co-infected individuals comparing across HCV strata.

As previously reported by EuroSIDA and others [1, 3, 23], we found the lowest rates of CKD in those who were anti-HCV negative or those with spontaneous clearance of HCV -RNA , as well as traditional factors associated with CKD, including age, hypertension, diabetes and the use of potentially nephrotoxic ARVS, as reported by many previous studies [24-26]. Cure of HCV with treatment has a number of benefits, including a reduction on both all cause and liver related mortality[27]. We were not able to demonstrate that HCV cure resulted in lower rates of CKD, consistent with previous studies[12-14] which had smaller populations and less power, or which considered decline in eGFR rather than CKD. Our study defined CKD rigorously using a confirmed eGFR < 60 ml/min/1.73m^2 over a period of 3 months. Slopes or rate of change in eGFR is arguably less clinically relevant than the definition used here. Our study also adjusted for a number of important confounding variables. HIV-associated nephropathy, membranous nephropathy and membranoproliferative glomerulonephritis are sometimes found at biopsy in HIV and HCV coinfected persons [28-30] and more studies on the role of HIV-infection, HCV coinfection, HCV-RNA and cure of HCV-RNA on these pathologies is warranted. The role of HCV in extrahepatic comorbidities is not fully understood, but may be related to the direct effect of HCV, immune activation or indirect effects such as drug and alcohol use [27].

In the pre-DAA era, there was some evidence in HCV monoinfected persons that interferon-based HCV treatment improved renal function and decreased the risk of CKD [31-33]. More recently, a study from Taiwan in monoinfected persons suggested a small decrease in renal function in persons treated with DAAs, although the changes were thought to be clinically insignificant [34]. The results from previous studies are difficult to compare to our findings. Although some were large studies, not all had information on HCV treatment outcomes, baseline eGFR, pre-dated the introduction of DAAs or included specific subgroups, such as those with cirrhosis. In addition, the contribution of different factors in coinfected individuals, including lifestyle factors, socioeconomic status and mechanisms other than HCV replication, may play a role in the development of CKD [35-37].

We found the highest rates of CKD in those cured, although they were not significantly higher than those with chronic hepatitis C or those who were HCV-RNA positive following HCV treatment. There are several possible reasons for our findings. Our study includes coinfected persons and follow-up to the middle of 2018. DAA treatment in EuroSIDA began to increase most notably around 2015 [22]; prior to this it is likely that the healthiest persons were selected for interferon treatment. Following 2015, those with F3/F4 liver fibrosis and more advanced liver disease were prioritized for DAA treatment. Those cured were also less likely to reverse their CKD and the proportion of follow-up with an eGFR > 90 ml/min/1.73m^2 was lowest, possibly suggesting a higher risk for renal disease. More of those cured developing CKD had a prior diagnosis of ESLD and those developing CKD in both those treated and cured and HCV-RNA positive following treatment were more likely to have been treated with interferon plus ribavirin. While we have adjusted for a wide range of confounders, it is possible that our findings reflect confounding by indication and further follow-up of persons treated with new generation DAAs is warranted.

Our study has a number of limitations. First and foremost, our data are from a cohort study and while we have defined 5 distinct HCV strata based on single values of Anti-HCV tests and HCV-RNA, comparisons across these strata are limited by our ability to adjust for differences as well as the possibility of unknown or unmeasured confounding that we cannot adjust for. We were not able to adjust for duration of HCV infection which may be an important confounder. As in a previous study [38], we chose not to define SVR according to treatment guidelines [21] in part due to differences between the many centres in EuroSIDA in frequency of HCV-RNA monitoring following treatment. Persons HCV-RNA positive after treatment, the individual may have only recently started treatment and with additional follow-up may be cured and move into this stratum. DAA regimens including sofosbuvir/ledipasvir and sofosbuvir/velpatasvir have been shown to increase the plasma concentration of tenofovir, especially when used with a boosted protease inhibitor [39], but we were not able to investigate an interaction between DAAs and tenofovir due to limited power. The strength of our study is that it is one of the largest of coinfected persons reported to date, with an extensive quality assurance and data monitoring program.

Although HCV-RNA positive persons have previously been shown to have higher rates of CKD, curing HCV with HCV treatment was not associated with a lower rate of CKD in this study. Further long-term follow-up is required to investigate the role of DAAs as their use becomes widespread to determine if the higher rates seen in this study were due to underlying high risk of CKD and new DAAs being targeted at the sickest individuals.

Table 1 Characteristics at baseline

		All		Anti-HCV negative Group 1		HCV antibody positive							
						Group 2 Spontaneous clearers		Group 3 Chronic untreated infection		Group 4 Cured		Group 5 treated; HCV-RNA positive	
		N	%	N	%	N	%	N	%	N	%	N	%
All		14754	100.0	9273	62.9	696	4.7	3021	20.5	922	6.2	842	5.7
Gender	M	10917	74.0	7023	75.7	454	65.2	2125	70.3	694	75.3	621	73.8
	F	3837	26.0	2250	24.3	242	34.8	896	29.7	228	24.7	221	26.2
HIV risk	MSM	5762	39.1	4856	52.4	103	14.8	393	13.0	241	26.1	169	20.1
	IDU	3588	24.3	245	2.6	391	56.2	1974	65.3	485	52.6	493	58.6
	Het	4300	29.1	3503	37.8	128	18.4	437	14.5	118	12.8	114	13.5
	Other	1104	7.5	669	7.2	74	10.6	217	7.2	78	8.5	66	7.8
Ethnic	White	12562	85.1	7776	83.9	565	81.2	2763	91.5	745	80.8	713	84.7
Origin	Other	2192	14.9	1497	16.1	131	18.8	258	8.5	177	19.2	129	15.3
Region	South	3773	25.6	2094	22.6	161	23.1	880	29.1	299	32.4	339	40.3
	Central	3939	26.7	2594	28.0	234	33.6	534	17.7	340	36.9	237	28.1
	North	3186	21.6	2332	25.1	127	18.2	483	16.0	136	14.8	108	12.8
	Central East	2041	13.8	1273	13.7	85	12.2	543	18.0	59	6.4	81	9.6
	East	1407	9.5	632	6.8	83	11.9	536	17.7	84	9.1	72	8.6
	Argentina	408	2.8	348	3.8	6	0.9	45	1.5	4	0.4	5	0.6
HBV status	Negative	12631	85.6	8218	88.6	524	75.3	2430	80.4	772	83.7	687	81.6
	Positive	1128	7.6	690	7.4	119	17.1	207	6.9	61	6.6	51	6.1
	Unknown	995	6.7	365	3.9	53	7.6	384	12.7	89	9.7	104	12.4
Ever cART	No	1703	11.5	1171	12.6	55	7.9	309	10.2	87	9.4	81	9.6
	Yes	13051	88.5	8102	87.4	641	92.1	2712	89.8	835	90.6	761	90.4
HIV VL	<500	11165	75.7	6801	73.3	563	80.9	2277	75.4	813	88.2	711	84.4
	>500	3589	24.3	2472	26.7	133	19.1	744	24.6	109	11.8	131	15.6
Comorbidities	AIDS	3838	26.0	2541	27.4	189	27.2	771	25.5	159	17.2	178	21.1
	CVD	410	2.8	282	3.0	23	3.3	56	1.9	32	3.5	17	2.0
	NADM	337	2.3	201	2.2	23	3.3	64	2.1	29	3.1	20	2.4
	ESLD	203	1.4	50	0.5	12	1.7	75	2.5	31	3.4	35	4.2
	Hypertension	3969	26.9	2689	29.0	178	25.6	630	20.9	253	27.4	219	26.0
	Diabetes	743	5.0	486	5.2	35	5.0	107	3.5	56	6.1	59	7.0

Table 1 Characteristics at baseline (ctd)

		All		Anti-HCV negative Group 1		HCV antibody positive Group 2 Spontaneous clearers		Group 3 Chronic untreated infection		Group 4 Cured		Group 5 treated; HCV-RNA positive	
		N	%	N	%	N	%	N	%	N	%	N	%
All		14754	100.0	9273	62.9	696	4.7	3021	100	922	100	842	100
Smoking status	Never	4299	29.1	3478	37.5	103	14.8	403	13.3	164	17.8	151	17.9
	Current	7380	50.0	3949	42.6	444	63.8	2047	67.8	472	51.2	468	55.6
	Previous	1896	12.9	1241	13.4	93	13.4	322	10.7	127	13.8	113	13.4
	Unknown	1179	8.0	605	6.5	56	8.0	249	8.2	159	17.2	110	13.1
Liver Fibrosis	0/1	7270	49.3	4025	43.4	475	68.2	1751	58.0	576	62.5	443	52.6
	2	492	3.3	37	0.4	23	3.3	206	6.8	110	11.9	116	13.8
	3	245	1.7	16	0.2	6	0.9	96	3.2	67	7.3	60	7.1
	4	484	3.3	44	0.5	26	3.7	197	6.5	96	10.4	121	14.4
	Unknown	6263	42.4	5151	55.5	166	23.9	771	25.5	73	7.9	102	12.1
D:A:D CKD score	Low	4422	30.0	3532	38.1	99	14.2	605	20.0	98	10.6	88	10.5
	Medium	5089	34.5	2899	31.3	294	42.2	1288	42.6	279	30.3	329	39.1
	High	5243	35.5	2842	30.6	303	43.5	1128	37.3	545	59.1	425	50.5
Prior HCV Treatment*	IFN + RBV	1441	81.7							724	78.5	717	85.2
	DAA + IFN	181	10.3							117	12.7	64	7.6
	DAA only	275	15.6							186	20.2	89	10.6
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age	years	43	37–51	43	36–51	44	38–51	41	35–47	48	41–53	46	40–52
CD4	/mm^3	470	318–669	461	320–653	484	344–714	440	282–643	558	376–782	543	370–741
Nadir CD4	/mm^3	174	70–281	176	70–283	163	57–280	164	71–273	182	79–286	190	99–282
Baseline	Mm/yy	10/06	7/04–6/12	11/05	6/04–11/08	10/12	1/05–2/15	02/10	12/04–11/14	11/14	7/14–6/15	10/14	7/08–5/15

Baseline was defined as the first prospective visit in EuroSIDA after 1/1/2004 at which both eGFR and HCV serostatus were measured, and where HCV-RNA was known for those Anti-HCV positive . Spontaneous clearers (HCV antibody positive, HCV-RNA negative, untreated); chronic untreated infection (HCV antibody positive, HCV-RNA positive, untreated); cured (HCV antibody positive, HCV-RNA negative, treated); treated, HCV-RNA positive (HCV antibody positive, HCV-RNA positive, treated). IFN; interferon. RBV; ribavirin. DAA; direct acting antivirals. *45 persons had previously been exposed to both IFN+RBV and DAA+IFN, 81 to both IFN+RBA and DAA only, 11 to DAA+IFN and DAA only, and 11 to IFN+RBV, DAA+INF and DAA only. All $p<0.0001$ except prior NADM ($p=0.12$), prior CVD ($p=0.0029$), nadir CD4 ($p=0.0051$), and HCV treatment with DAA+IFN ($p=0.0004$). Characteristics of individuals were compared across strata using chi-squared statistics for categorical variables and the Kruskall-Wallis test for continuous variables

Table 2 Crude incidence rates of CKD stratified by current HCV strata

		HCV ab status	HCV-RNA	HCV treatment	Events	PYFU	Rate / 1000 PYFU	95% CI
Total					1128	115335	9.8	9.2–10.4
Group 1	Anti-HCV negative	Negative	n/a	n/a	814	82523	9.9	9.2–10.5
Group 2	Spontaneous clearers	Positive	Negative	Untreated	42	4854	8.7	6.0–11.3
Group 3	Chronically infected	Positive	Positive	Untreated	125	14516	8.6	7.1–10.1
Group 4	Successfully treated	Positive	Negative	Treated	109	8479	12.9	10.4–15.3
Group 5	treated; HCV-RNA positive	Positive	Positive	Treated	38	4963	7.7	5.2–10.1

PYFU; person years of follow-up. CI confidence interval

Table 3 Characteristics at CKD or last visit in cured and HCV-RNA positive following treatment

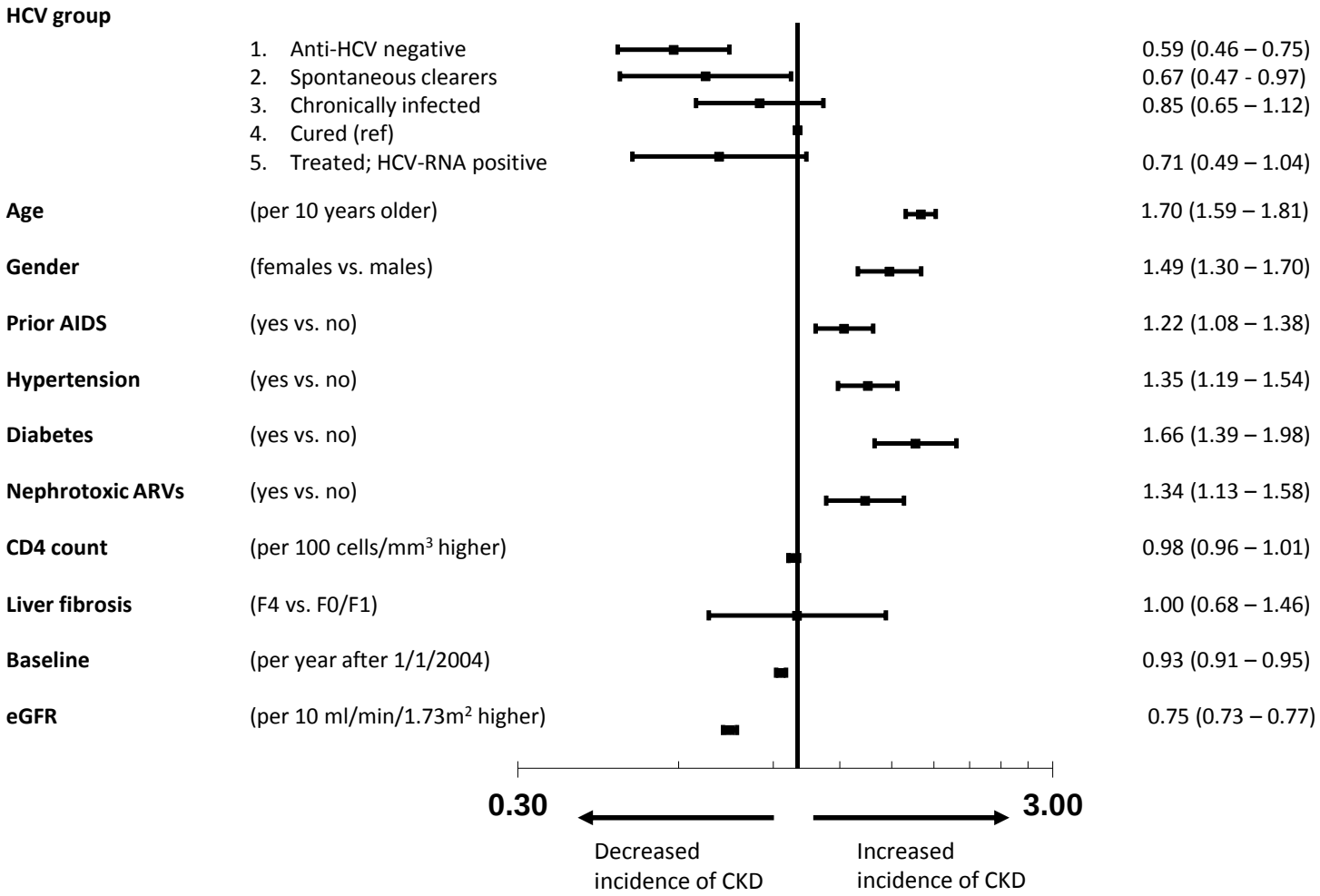
		All		Group 4; cured				Group 5; treated; HCV-RNA positive			
				No CKD		CKD		No CKD		CKD	
		N	%	N	%	N	%	N	%	N	%
All		3231	100	2553	79.0	109	3.4	531	16.4	38	1.2
Gender	M	2415	74.7	1929	75.6	76	69.7	387	72.9	23	60.5
	F	816	25.3	624	24.4	33	30.3	144	27.1	15	39.5
HIV risk	MSM	716	22.2	596	23.3	23	21.1	90	16.9	7	18.4
	IDU	1819	56.3	1413	55.3	62	56.9	320	60.3	24	63.2
	Het	444	13.7	349	13.7	13	11.9	78	14.7	4	10.5
	Other	252	7.8	195	7.6	11	10.1	43	8.1	3	7.9
HBV status	Negative	2672	82.7	2102	82.3	93	85.3	447	84.2	30	78.9
	Positive	208	6.4	169	6.6	9	8.3	26	4.9	4	10.5
	Unknown	351	10.9	282	11.0	7	6.4	58	10.9	4	10.5
HIV VL	<500 copies/ml	3116	96.4	2486	97.4	106	97.2	488	91.9	36	94.7
Comorbidies	ESLD	104	3.2	76	3.0	12	11.0	15	2.8	1	2.6
Liver	0/1	2018	62.5	1592	62.4	67	61.5	331	62.3	28	73.7
Fibrosis	2	451	14.0	363	14.2	10	9.2	75	14.1	3	7.9
	3	289	8.9	234	9.2	9	8.3	42	7.9	4	10.5
	4	446	13.8	346	13.6	19	17.4	78	14.7	3	7.9
	Unknown	27	0.8	18	0.7	4	3.7	5	0.9	0	0.0
Prior HCV	IFN + RBV	1393	43.1	959	37.6	56	51.4	347	65.3	31	81.6
Treatment	DAA + IFN	189	5.8	168	6.6	4	3.7	16	3.0	1	2.6
	DAA only	1649	51.0	1426	55.9	49	45.0	168	31.6	6	15.8
	SOF/RBV	85	5.2	80	5.6	2	4.1	3	1.8	0	0.0
	SOF/DCV	241	14.6	206	14.4	14	28.6	20	11.9	1	16.7
	SOF/SMV	51	3.1	47	3.3	3	6.1	1	0.6	0	0.0
	SOF/LDV	678	41.1	595	41.7	14	28.6	67	39.9	2	33.3
	OBV/PTV	56	3.4	52	3.6	0	0.0	4	2.4	0	0.0
	OBV/PTV/DSV	167	10.1	146	10.2	6	12.2	14	8.3	1	16.7
	GZR/EBR	151	9.2	128	9.0	5	10.2	17	10.1	1	16.7
	SOF/VEL	141	8.6	105	7.4	4	8.2	31	18.5	1	16.7
	GLE/PIB	56	3.4	46	3.2	0	0.0	10	6.0	0	0.0
	Other	23	1.4	21	1.5	1	2.0	1	0.6	0	0.0

Table 3 Characteristics at CKD or last visit in cured and HCV-RNA positive following treatment

		All		Group 4; cured				Group 5; treated; HCV-RNA positive			
				No CKD		CKD		No CKD		CKD	
		N	%	N	%	N	%	N	%	N	%
All		3231	100	2553	79.0	109	3.4	531	16.4	38	1.2
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age	years	52	45–57	52	45–57	54	50–58	49	42–54	52	47–59
CD4	/mm^3	614	444–628	628	460–853	600	442–830	560	399–785	481	390–818
Baseline	Mm/yy	09/14	04/06–04/15	10/14	06/08–05/15	02/14	09/04–12/14	12/10	11/04–12/14	07/04	04/04–12/14
Nadir CD4	/mm^3	180	80–283	180	81–285	148	60–260	180	84–281	144	60–214
Yrs since first HCV treatment started		5.6	2.6–10.3	5.6	2.6–10.4	5.6	1.9–10.2	5.8	2.3–10.1	7.8	4.3–10.0
Months since last HCV treatment started		3.4	1.8–7.0	3.3	1.8–6.6	3.1	1.5–7.8	4.5	1.4–8.6	5.5	2.2–8.6

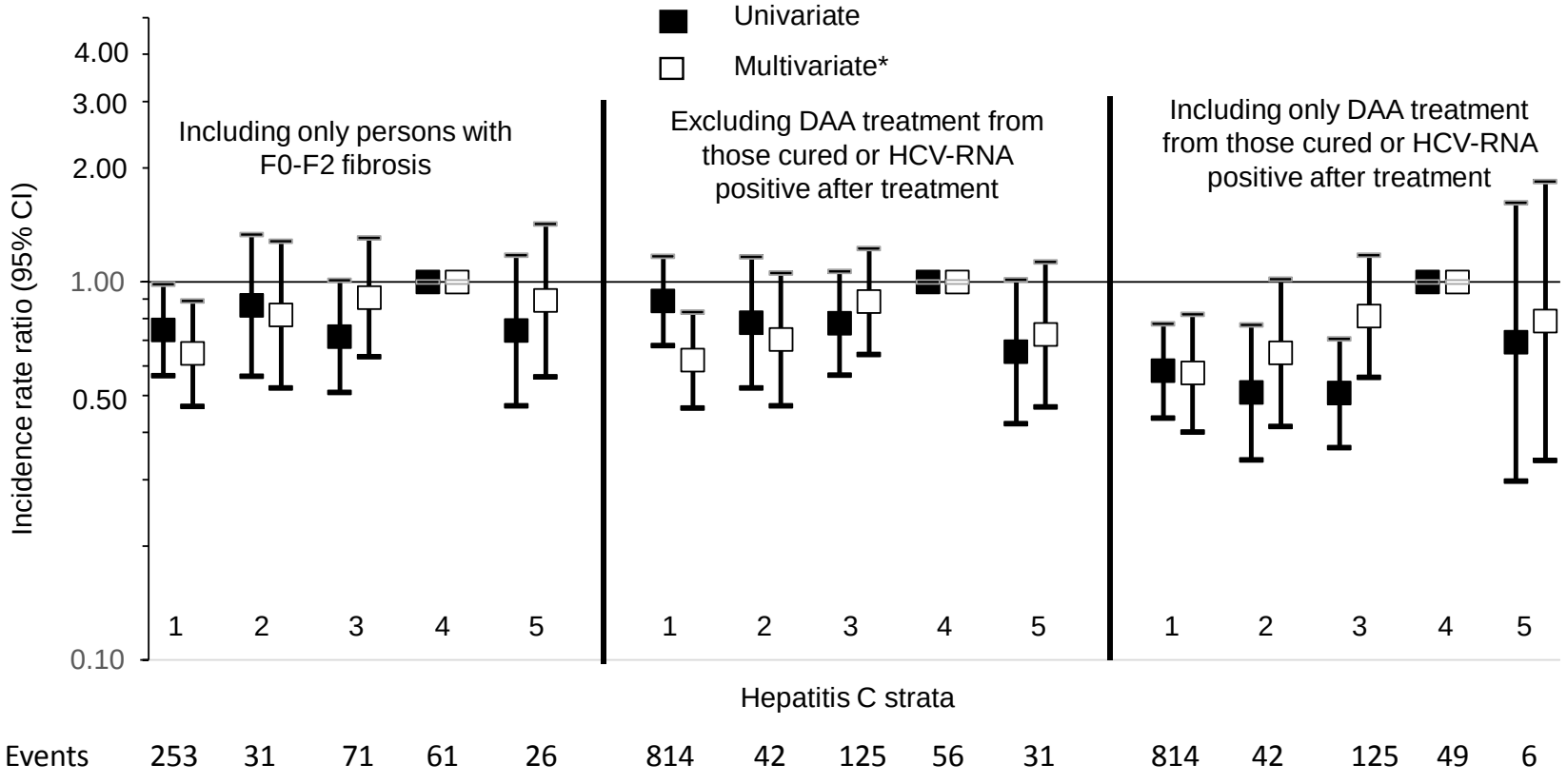
Baseline was defined as the first prospective visit in EuroSIDA after 1/1/2004 at which both eGFR and HCV serostatus were measured, and where HCV-RNA was known for those Anti-HCV positive. INF; interferon. RBV; ribavirin. DAA; direct acting antivirals. SOF; sofosbuvir. DCV; daclatasvir. SMV; simeprevir. LDV; ledipasvir. OBV; ombitasvir; PTV; paritaprevir. DSV; dasabuvir. GZR; grazoprevir. EBR; elbasvir. VEL; velpatasvir; GLE; glecaprevir. PIB; pibrentasvir

Figure 1
Multivariate incidence rate ratios of CKD



All factors are included at baseline with the exception of HCV group. *Model additionally adjusted for starting integrase inhibitors as a time-updated variable

Figure 2
Univariate and multivariate* incidence rate ratios of CKD: Sensitivity analyses



HCV status	*HCV RNA*	*HCV treatment*		*Group*
Negative	Negative	N/A	Anti-HCV negative	1
Positive	Negative	Untreated	Spontaneous clearers	2
Positive	Positive	Untreated	Chronic infection	3
Positive	Negative	Treated	Cured	4
Positive	Positive	Treated	Treated; HCV-RNA positive	5

*Adjusted for eGFR, use of nephrotoxic ARV, AIDS, hypertension, diabetes, baseline CD4, age, liver fibrosis stage and baseline date, all at baseline and starting integrase inhibitors as a time-updated variable

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Appendix

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Abstract

Background: Hepatitis C virus (HCV) infection has been associated with increased risk of chronic kidney disease (CKD). We investigated the impact of HCV cure on CKD in HIV-positive persons in the EuroSIDA study.

Methods: HIV-positive persons with known HCV status and ≥3 serum creatinine measurements after 1/1/2004 were compared based on time-updated HCV-RNA and HCV treatment: Anti-HCV negative, spontaneously cleared HCV, Chronic untreated HCV, successfully treated HCV and HCV-RNA positive after HCV treatment. Poisson regression compared incidence rates of CKD (confirmed [>3 months apart] eGFR < 60 ml/min/1.73m^2) between HCV strata.

Results: 14754 persons were included; at baseline 9273 (62.9%) were HCV-Ab negative, 696 (4.7%) spontaneous clearers, 3021 (20.5%) chronically infected, 922 (6.2%) successfully treated and 842 5.7%) HCV-RNA positive after treatment. During 115335 person-years of follow-up (PYFU), 1128 (7.6%) developed CKD; crude incidence 9.8/1000 PYFU (95% CI 9.2–10.4). After adjustment, persons Anti-HCV negative (adjusted incidence rate ratio [aIRR] 0.59; 95% CI 0.46-0.75) and spontaneous clearers (aIRR 0.67; 95% CI 0.47-0.97) had significantly lower rates of CKD compared to those cured while persons chronically infected (aIRR 0.85; 95% CI 0.65-1.12) and HCV-RNA positive after treatment (aIRR 0.71; 95% CI 0.49-1.04) had similar rates. Analysis in those without F3/F4 liver fibrosis using a more rigorous definition of CKD showed similar results.

Conclusions: This large study found no evidence that successful HCV treatment reduced CKD incidence. Confounding by indication, where those with highest risk of CKD were prioritized for HCV treatment in the DAA era, may contribute to these findings.

We thank all the reviewers for their careful review of the manuscript and our detailed responses to these comments appear below. Where we refer to a page number please note it refers to the manuscript using track changes.

Reviewers' comments:

Reviewer #1: SUMMARY
This is a complicated, confusing and difficult to read analysis of the EuroSIDA database which examines a hypothesis that is tenuous, i.e. that PLHIV with co-infection with HCV are more likely to experience CKD and that those treated for HCV successfully will therefore be less likely to experience CKD. While there are well recognised extra-hepatic manifestations of HCV (e.g. glomerulonephritis), these are rare and at a population level are unlikely to make any clinically meaningful difference to renal outcome in people with HIV/HCV co-infection.

We thank reviewer 1 for his comments.

MAJOR COMMENTS
The study hypothesis is weak - it is not at all clear that HCV co-infection itself is causally related to CKD. While there are a number of extra-hepatic manifestations of HCV and evidence that eradicating HCV can improve renal function in people experiencing those complications, e.g. those with HCV-associated glomerulonephritides and membranous nephropathy (rare complications), cohort studies (in which the vast majority of those with HCV likely have no extra-hepatic pathology) have not shown any benefit in renal function. It is therefore not clear why this group embarked on this study as it would seem that the most likely hypothesis should be that there is no association. This should be reflected in the Discussion and the Conclusion to the abstract, i.e. that it may well be that at a population level HCV coinfection in general exerts no influence on renal function at all.

We agree that renal diseases with a documented causal role of HCV are uncommon and likely to make little or no difference at a population level, but the impact of HCV-related systemic inflammation and risk of CKD (and CVD and cancer) remain unclear, as in the recent review from Henson et al [1]. As we have noted, a meta-analysis clearly shows an association between HCV coinfection and CKD [2], while we have shown an association with chronic infection and CKD in different populations[3, 4]. It is possible therefore that clearing HCV RNA via treatment of HCV may reduce the incidence of CKD. We would also argue that even if previous studies have not found a strong relationship, methodological issues or lack of power leaves room for a well designed and larger study such as the one we present.

We have highlighted these points in the introduction (p3, paragraph 1 and 3) and discussion (p11, paragraph 2) to make the rationale for our study stronger but have not amended the abstract as reviewer #4 asked for additional details to also be included into the abstract.

As per all cohort studies, the study has significant power to make spurious findings that are biased and/or confounded. The main finding that PLHIV with HCV that have been successfully cleared are more likely to experience CKD is a good example - as the authors discuss, this is most likely a

spurious finding by way of bias by indication. As the authors state in the Introduction, cohort studies have been unable to document an improvement in renal function in those with HCV and an SVR to treatment compared to those without SVR to treatment. If HCV doesn't influence renal function this shouldn't be a surprise.

The authors split the cohort into 5 separate groups. While this makes some sense, each group is likely to have specific characteristics that make comparisons across those 5 groups fraught (e.g. there are likely to be all sorts of known and unknown differences between people with HCV coinfection and those HCV negative). As such any conclusions based on these comparisons are difficult to take (in fact shouldn't be taken) at face value.

We have combined the response to the above 2 points into 1.

We completely agree with the reviewer regarding the limitations of cohort studies, and the difficulties of interpreting such data for exactly the reasons the reviewer raised. We agree that one explanation for our findings are confounding by indication, as we have clearly stated in the abstract and in the discussion on page 11 (paragraph 1) as well as the final conclusion of the paper. We have added a sentence to the limitations of the discussion (page 12, paragraph 2) regarding cohort studies in general but we have not made other changes in response to these comments as we believe our interpretation of the data is quite conservative and would disagree that we show persons successfully treated for HCV have higher rates of CKD, this finding is not statistically significant.

In addition, the division of the cohort into the 5 groupings makes it very difficult for the reader to easily follow the results. This is particularly the case when the groups are referred to by number and not by group description. I would recommend that the group description be used throughout the manuscript (at the moment this is variable).

We have carefully checked and amended and used the description of the group throughout the manuscript.

The results section informs us that of 5 models tested, the manuscript focuses on the results of model 3 which adjusted for baseline fibrosis (one assumes hepatic in this case). How was fibrosis assessed and quantified? What hypothesis or pathophysiological knowledge drove the thinking behind the creation of model 3?

The reviewer is correct that we are referring to baseline fibrosis, this has been clarified throughout the manuscript and in the footnote to Figure 2. We have defined fibrosis consistently across all EuroSIDA studies, and have referenced this study in the manuscript (page 6, paragraph 1). In brief, data on alanine transaminase (ALT), aspartate transaminase (AST) and platelet counts have been collected in individuals enrolled in the cohort since 1999 and 2005, respectively, and were used to calculate the AST to platelet ratio index (APRI) as a marker for liver fibrosis. Data on liver biopsy and Fibroscan have been collected since 2010, with clinical sites requested to list all previous test results where liver biopsy was graded using the METAVIR scoring system, and return the histological report for internal validation. Plasma hyaluronic acid (HA) has been measured in all HCVAb positive individuals with stored plasma samples available. The table below summarises the cut-offs used to define fibrosis in this study, which is consistent with our previous publications. This information is not included in the manuscript currently due to space constraints but we are happy to add it if the editor feels it is appropriate.

Metavir liver biopsy	*F0*	*F1*	*F2*	*F3*	*F4*
Fibroscan	*<7.6*		*7.6 – 9.5*	*9.6 – 12.5*	*>12.5*
APRI	*<1.5*		*1.5 – 1.75*	*1.75 – 2*	*>2*
HA	*<100*		*100-250*		*>250*

Our model building strategy is described in the methods. Our group has published extensively on CKD in HIV infected persons and developed a risk score for predicting CKD [5] which we hypothesised would be an accurate predictor of CKD in those with known HCV status. This formed the basis of our first model, adjusting additionally for fibrosis stage. This first model adjusted for the score rather than the components of the score. In order to fully scrutinise our data, we tried model 2 which adjusted for many additional things, to try and address some of our concerns about differences between groups, as highlighted by reviewer 1 above. Our third model was similar to model 1, but rather than adjusting for the risk score, adjusted for the factors included in the risk score which have been shown by us and others to be predictive of CKD. This model additionally adjusted for liver fibrosis and use of integrase inhibitors. We have expanded our rationale for these 3 models in the statistical methods (page 6, paragraph 1). The results of these models are included in the response to reviewer 4 for transparency.

We are also informed that model 3 was preferred because '…it had the lowest Akaike score.' Please explain the score and why this made model 3 'preferred'?

The Akaike Information Criteria is a standard methodology for comparing goodness of fit in statistical models, where a lower score indicates a better fitting model. The AIC measured both the goodness of fit and the simplicity of the model, and thus deals with both under and over fitting of statistical models[6]. We have not added to the methods regarding this point as we believe it is clear as is and the AIC is well accepted statistical term.

One assumes that of course model 3 was preferred after the results were produced, seen and discussed. Was there any thought of choosing one model a priori in the stats analysis plan prior to database lock? A copy of that plan would be useful to review.

This was not the case and this is not the way EuroSIDA conducts analyses. Our analyses are rigorous, conservatively interpreted and with many sensitivity analyses to investigate the robustness of our results. Our final model was selected on the basis of goodness of fit as described in the previous response. All models are shown in a Table below in response to reviewer 4. All EuroSIDA analyses have approved project proposals including a statistical analysis plan which is subject to review and approval from the EuroSIDA scientific steering committee.

Those with HCV coinfection were chosen as the primary comparator group for the main tests. Why not use the HCV Ab negative group for primary comparison?

We chose those cured as the reference group for consistency with our previous work [7] and because we wished to compare incidence rates of CKD to those cured rather than those who were anti-HCV negative. We have kept the reference group as is.

MINOR COMMENTS

A significant proportion of the cohort actually reverted to an eGFR >60 ml/min/1.73m2 after qualifying as 'CKD' by study definition (~39%). It isn't clear how these participants were handled in the analysis. Please explain.

This was a secondary analysis where the starting point, or baseline, was CKD. In the primary analysis persons were censored at last eGFR or development of CKD, as stated in the methods (page 5, paragraph 1). For the secondary analysis of returning to a normal eGFR, individuals were censored at last eGFR. This has been clarified in the methods (page 4, paragraph 2)

Those treated for HCV received a mix of interferon-containing and non-containing regimens. Given the substantially different outcomes between these treatments, was there any thought of analysing accordingly?

Some of this data was already included in the results (page 9, paragraph 3) as a sensitivity analysis, and we have expanded this and added this data to figure 2.

Reviewer #2: In this manuscript Mocroft and colleagues study the impact HCV treatment cure on chronic kidney disease (CKD) in HIV/coinfected patients. The authors do not find a reduction in CKD among HCV cured patients. Overall, the paper is interesting, straightforward and well performed. This reviewer does not have important concerns regarding this study. It is intriguing why HCV cured individuals had a higher incidence of CKD than HCV positive or HCV treated and failing patients, authors may speculate a little bit around this issue.

Thanks for this positive review. The manuscript has changed significantly according to suggestions from reviewer 1 including around confounding by indication.

Minor point

In the statistical methods section there are several writing errors, please check more carefully this methods section. Inclusion of page numbering and/or line numbering may have helped here.

We have checked and amended as requested and added page numbers.

Reviewer #3: Summary: In this study, the authors investigated the incidence of chronic kidney disease (CKD) in HCV/HIV co-infected persons divided into five HCV groups: 1) anti-HCV negative, 2) spontaneously cleared HCV, 3) chronically infected HCV, 4) cured HCV, and 5) treated but HCV-RNA+. This was a large, multi-cohort European study, with 14,754 persons and 115,335 person-years of follow-up (PYFU). They did not find any evidence for decreased incidence of CKD among HCV-cured persons (group 4). The study adjusted for a variety of potential confounders (using 3 different multivariate models) and conducted several sensitivity analyses, all showing similar results.

Minor Comments:

1. The introduction states that "while declines in eGFR might be useful to study short term changes in renal function, a more rigorous definition of renal decline, such as CKD, has greater clinical relevance". The discussion likewise states that "our study defined CKD rigorously and did not consider changes in eFGR which are arguably less clinically relevant". However, in the

methods, it is clear that your definition of CKD is based on eGFR - just a specified <60/mL/min/1.73m2 threshold. Please clarify this in the introduction/discussion.

Thank you for this comment. We meant to draw a distinction between studies that have used eGFR slopes as an endpoint, compared to those that use the KDIGO endpoint of CKD [8], requiring 2 eGFRs < 60 at least 3 months apart. We have clarified in the introduction (page 3, paragraph 2 and page 11, paragraph 2).

2. Results, the last sentence of paragraph 2 provides number of individuals with DAA+IFN or DAA only, but what about the rest of the 1764 previously treated individuals (the math for IFN vs DAA does not match). Please clarify.

Persons could have been exposed to more than 1 HCV treatment prior to our study baseline. We have added a footnote to the Table 1 to clarify this.

3. In the sensitivity analysis results, an aIRR is given for group 4, which should be the reference group? Please either provide aIRR for groups 1 and 2 in the sensitivity analysis or also include group 4 aIRR in the main results for clearer comparison.

We have clarified this sentence as requested (page 9, paragraph 3), but have not added the other groups as requested as the data is included in Figure 2.

4. For the discussion - it is also likely that length of chronic HCV / HIV infection impacts risk of CKD, which would be important to mention as another possible confounder (e.g. individuals who previously had IFN treatment and now have DAA treatment might be expected to have had chronic HCV for longer).

Thanks for this point, we have added it to the discussion (page 12, paragraph 2)

5. Table 3, would be nice to also have p-values for the characteristics.

We have not added the p-values to table 3 as requested, there are multiple comparisons here that could be made (within those cured or those HCV-RNA positive after treatment, or comparing those with and without CKD, or across all 4 strata). We have however rewritten the paragraph describing these results which was not easy to follow (page 10, paragraph 3).

6. Please be sure to define all abbreviations at first use, including eGFR, D:A:D CKD risk score, and ESLD.

We have carefully reviewed the manuscript and hope all abbreviations are now spelt out appropriately.

Reviewer #4: Summary of comments: The topic of the paper is an important one but I struggled to understand much of the methods and many of the assumptions that underlie the analysis.

We hope that in addition to specific responses below our other clarifications and changes have made the manuscript easier to read.

Abstract (results):

Although the authors include the number of participants who were HCV-positive at baseline (n=5481), they do not provide the sample sizes or person years for sub-groups 2-5 separately. I appreciate that one can guess at the sample sizes of the sub-groups by the widths of the 95% CIs, but it would be helpful not to have to guess while reading the abstract.

We have added this information to the abstract as requested.

Introduction

Author text: "Hepatitis C (HCV) coinfection…"

Comment: There is a typo - this should be "Hepatitis C virus (HCV) coinfection….."

Amended as requested.

Author text: "Some studies found those with chronic HCV infection had higher rates of chronic kidney disease…."

Comment: It is unclear if the "rate" is the correct word here. In reference 2 the authors present ORs for repeated measures. I am not aware that such a measure could be interpreted as a rate.

We have amended this.

Author text: "cohort studies, where most of the patients have no known underlying renal pathology, have been unable to document an improvement in kidney function…."

Comment: Sample sizes of treated participants included in these cohort studies would be helpful.

We have added the number with SVR to the introduction as requested (page 3, paragraph 2).

Author text: "One further study reported a marginally significant protective effect of SVR on CKD [16], but did not adjust for baseline renal function."

Comment: In this reviewer's opinion, there is no such thing as a marginal association. Either the p-value was <0.05 or it wasn't.

We have amended the text to reflect this comment (page 3, paragraph 2).

Author text: "Changes in renal function in these studies was measured in a variety of ways, and while declines in eGFR might be useful to study short term changes in renal function, a more rigorous definition of renal decline, such as CKD, has greater clinical relevance given its association with other clinical events, such as cardiovascular disease [17]."

Comment: I find this text confusing. At first I thought from this text that the prior studies only looked at declines in eGFR that did not meet the criteria for CKD. However, the abstract of reference #15 suggests that those authors did look at CKD. It would be clearer if the authors were

specific about the renal phenotype definitions used in prior studies and explain how the renal phenotypes to be used in in the current study are similar or different.

We have clarified this text also in response to the comment from reviewer 2 (page 3, paragraph 2 and page 11, paragraph 2).

Methods

Author text: "Baseline was defined as latest of 1 January 2004, first eGFR, enrolment in EuroSIDA, known HCV serostatus and for those anti-HCV positive, known HCV-RNA status."

Comment: I find this text confusing. Perhaps something like "the first visit at which both eGFR and HCV serostatus were measured". But perhaps I'm misunderstanding.

We have amended the text as requested (page 4, paragraph 2).

Author text: "Persons aged < 16 at baseline or without a CD4 count and HIV viral load in the 12 months before or 1 month after baseline were excluded."

Comment: It seems odd to include a CD4 count 12 months before but only 1 month after the baseline visit. Does something happen at the baseline visit that would affect the CD4 count?

No, but we would be concerned about introducing a survival bias by including information recorded a long time after baseline; it means the individual has to survive and stay under follow-up for long enough for a measurement to be taken. This has not been amended.

Author text: "Based on time-updated HCV antibody tests, HCV-RNA and HCV treatment, we defined 5 HCV groups: 1. Anti-HCV negative 2. HCV antibody positive, HCV-RNA negative, untreated (spontaneous clearers) 3. HCV antibody positive, HCV-RNA positive, untreated (chronic infections) 4. HCV antibody positive, HCV-RNA negative, treated (successfully treated with any HCV therapy; cured). 5. HCV antibody positive, HCV-RNA positive, treated (treated, HCV-RNA positive)"

Comment: It would be helpful to provide the reader with some information about the frequency and coverage of HCV testing in the cohorts contributing to EuroSIDA. For example, is spontaneous clearance always defined as a cross-sectional HCVAb+/HCV RNA- or have some cohorts conducted longitudinal testing with documented loss of HCV RNA. Would it be important to point out that the same participant can contribute person-time to multiple groups?

EuroSIDA collects information as performed at the clinics, and this is very heterogeneous within clinics, patient groups and across regions. We have added some text to the methods regarding our definitions (page 5, paragraph 2) as well as to the discussion (page 12, paragraph 2).

Author text: "Note that group 5 includes persons who did not achieve SVR, persons without an end of treatment response, persons who were HCV-RNA positive having started treatment more recently and those reinfected with HCV."

Comment: This group is very heterogeneous, including participants for whom treatment is underway.

We completely agree with the reviewer and this is one of the limitations of our analysis as noted (page 12, paragraph 2). We have not changed the manuscript further.

Author text: "Reversal of CKD was defined as a confirmed (> 3 months apart) increase in eGFR to > 60/ml/min/1.73m2 among persons with at least 2 further eGFRs after development of CKD and with
3 months follow-up after CKD."

Comment: Is this CKD reversal phenotype commonly used in the renal literature? It seems a little vague - why 2 further eGFRs and not 1 or 3? Would a participant have to have, say, GFRs of <60 for >=3 consecutive visits followed by GFR>60? I also find this reversal phenotype confusing because above the text states "Persons were followed until their last visit (median June 2018), date of death, or CKD, whichever occurred first." I thought the clock stopped at CKD? Is there a separate analysis and clock for the reversal phenotype?

We apologise for the confusion and this text has been amended also in response to reviewer 1 (page 5, paragraph 2). In terms of developing CKD, persons by definition need to have a minimum of 3 eGFRs to be included; the baseline one and 2 further measurements to define CKD. Persons may have more measurements but not less. The eGFR < 60 needs to be over a period of at least 3 months according to KDIGO guidelines[8] therefore if there is a 'blip' whereby the eGFR goes above 60 after being below, the 3 month period will start again on the next eGFR < 60.

Author text: "Incidence rates of CKD per 1000 person-years of follow-up (PYFU) were calculated within HCV groups, and Poisson regression was used to compare these rates with group 4 (cured) as the reference group."

Comment: As mentioned above, I would clarify for the reader that person-time from the same participant can be used in more than one group. Also, can the authors clarify why they are using Poisson regression and not Cox regression? To my understanding Poisson regression is useful when individual data are not available or if multiple events are being considered. In this analysis the authors are just looking at time to first incident CKD, death or administrative censoring - is this correct?

As noted above, we have clarified PYFU can be included in more than one group (page 5, paragraph 1). These analyses could have been performed using either Cox models or Poisson regression, the results should be consistent. We prefer Poisson regression as it lends itself more naturally to where there is an arbitrary baseline, such as in our study, while Cox regression is more appropriate when there is a well defined baseline (such as randomisation into a trial). Further, we find incidence rates and incidence rate ratios easier to interpret and explain than hazard rates. We have not changed the manuscript in response to this comment.

Author text: "Different models were investigated; the first adjusted only for the D:A:D CKD risk score [19] and baseline fibrosis stage (as previously described; [20]; this was included as measured at baseline as it
may lie on the causal pathway between HCV status and CKD)."

Comment: Looking at reference #19, isn't HCV status included in the D:A:D CKD risk score?

The reviewer is correct; the D:A:D risk score includes Anti-HCV status; in the first model which included the actual D:A:D risk score we have not included the HCV component and this is now clarified in the methods, (page 6, paragraph 1)

Author text: "The second model adjusted for many potential confounding factors at baseline (gender, HIV exposure group, region of Europe…."

Comment: It would be helpful if the authors would clarify which adjustment factors were time-updated (time varying) and which were fixed. This second model is also confusing because some elements (e.g., gender, HIV exposure group) are also part of the D:A:D CKD risk score.

This text has also been revised in view of comments from reviewer 1, we hope our model building strategy is now clearer. All variables described for model 2 were fixed at baseline, this has been clarified on page 6, paragraph 1, although we have also performed analyses where these were time-updated which are not discussed in the manuscript (but are presented in the Table below for complete transparency).

Author text: A third model adjusted for baseline fibrosis and the components of the D:A:D CKD risk score (including use of nephrotoxic ARVs) at baseline as separate variables.

Comment: I'm looking at Table 2 in reference #19 and I don't see nephrotoxic ARVs included. Am I looking in the correct place? Should I be interpreting this text differently?

In the D:A:D paper, the CKD risk score was built without nephrotoxic ARVs included, and then these were included to show the additional risk from these ARVs and what their contribution to the risk score would be.

Author text: "As results were consistent across models, our results focus on model 3 which had the lowest Akaike Information Criterion."

Comment: It is surprising that the results were consistent across models, given how different the list of adjustment factors is between, say, Model 1 and Model 2. I myself prefer nested models, and that way a formal likelihood ratio test can be conducted to assess for the optimal model. But I might compare AICs between models with identical covariates but different covariance structures. In the absence of supplementary material showing that these models are indeed nearly identical I find this modeling strategy to be fairly opaque.

This text has been revised also in response to Reviewer 1. The table below summarises the results from the 3 models described in the methods of the paper. We would not suggest adding these to the manuscript but are happy to include them as supplementary information if the reviewer or editor feels it is appropriate.

	Univariate				*Multivariate**			
Model 1	*IRR*	*Lower CL*	*Upper CL*	*p*	*IRR*	*Lower CL*	*Upper CL*	*p*
Anti-HCV negative	0.77	0.63	0.94	0.01	0.99	0.79	1.23	0.91
Spontaneous clearers	0.67	0.47	0.96	0.03	0.75	0.52	1.08	0.12
Chronically infected	0.67	0.52	0.87	0.00	0.86	0.66	1.12	0.25
Cured	1.00	-	-	-	1.00	-	-	-
HCV-RNA positive after treatment	0.60	0.41	0.86	0.01	0.76	0.52	1.10	0.14
Model 2								
Anti-HCV negative	0.77	0.63	0.94	0.01	0.58	0.44	0.76	0.00
Spontaneous clearers	0.67	0.47	0.96	0.03	0.58	0.40	0.84	0.00
Chronically infected	0.67	0.52	0.87	0.00	0.75	0.57	0.99	0.04
Cured	1.00	-	-	-	1.00	-	-	-
HCV-RNA positive after treatment	0.60	0.41	0.86	0.01	0.69	0.48	1.01	0.05
Model 3								
Anti-HCV negative	0.77	0.63	0.94	0.01	0.59	0.46	0.75	0.00
Spontaneous clearers	0.67	0.47	0.96	0.03	0.67	0.47	0.97	0.04
Chronically infected	0.67	0.52	0.87	0.00	0.85	0.65	1.12	0.24
Cured	1.00	-	-	-	1.00	-	-	-
HCV-RNA positive after treatment	0.60	0.41	0.86	0.01	0.71	0.49	1.04	0.08
Model 4 (all factors updated)								
Anti-HCV negative	0.77	0.63	0.94	0.01	0.60	0.47	0.77	0.00
Spontaneous clearers	0.67	0.47	0.96	0.03	0.68	0.47	0.98	0.04
Chronically infected	0.67	0.52	0.87	0.00	0.85	0.65	1.11	0.22
Cured	1.00	-	-	-	1.00	-	-	-
HCV-RNA positive after treatment	0.60	0.41	0.86	0.01	0.72	0.50	1.05	0.09

**Adjustments as per manuscript*

Author text: "We performed analyses where the last HCV RNA measurement was carried forward for a maximum of 12 months, ….."

Comment: I find this text confusing. The last HCV RNA measurement in whom? Aren't all HCV RNA data carried forward until CKD, death or administrative censoring? In other words, a person whose first HCV data available to EuroSIDA shows HCVAb+/HCV RNA- is always assumed to be in the spontaneous clearance group unless a new incident infection is documented - is this correct? Or for example, a person with an HCV RNA+ test in 2005 would be assumed to still be HCV RNA+ in 2015 if no treatment was received in the interim?

The reviewer's interpretation is correct and we refer to the HCV RNA being carried forward for a maximum of 12 months in our sensitivity analysis. We have changed the wording to clarify this (page 6 paragraph 2)

Author text: "excluding all follow-up and CKD events occurring after the development of F3/F4 fibrosis during follow-up, …"

Comment: What follow-up events aside from CKD are being excluded?

It is the PYFU which are excluded, and we have clarified this (page 7, paragraph 1)

Author text: "We also explore an alternative definition of CKD as a confirmed 25% decline to

<60/ml/min/1.73m2."

Comment: Has this phenotype been used previously in the renal literature?

Yes, by Mocroft et al; this has now been referenced in the methods (page 7, paragraph 1)[3].

Results:

Author text: "Compared to the 14754 included, the 1266 excluded were less likely to be MSM, were less likely to be from Central, or West Europe and more likely to be from Central East, Eastern Europe or
Argentina compared to southern Europe. They were also less likely to have suppressed HIV viral load and more likely to have a prior AIDS diagnosis."

Comment: There should be p-values or supplementary material presented to support these statements.

We omitted p-values as they are all highly significant given the size of our population. We have added to the results as requested (page 7, paragraph 1).

Author text: "Table 1 shows the characteristics of the 14754 included persons,….."

Comment: In the subscript of Table 1 I see the following text: "All p<0.0001 except prior NADM (p=0.12), prior CVD (p=0.0029), nadir CD4 (p=0.0051), and HCV treatment with DAA+IFN (p=0.0004)." No mention of these data are noted in the text. Does this mean that every characteristic shown in Table 1 was tested by ANOVA for differences across the 5 groups? Or something else?

As per our previous response, the study is large and therefore p-values are somewhat meaningless and the groups, by definition, are very heterogeneous as noted to reviewer 1. A long description of all the differences would make the results quite difficult to read, so we chose to highlight the key differences in the results (page 7, paragraph 2). Differences across the groups were tested using chi-squared for categorical variables and Kruskall-Wallis test for continuous variables as now noted in the methods (page 6, paragraph 1) and footnote to table 1.

Author text: "1764 persons had been previously treated for HCV; the majority of these (1467; 83.2%) had been treated with interferon plus ribavirin. At baseline, 181 had received a DAA plus interferon, and 275 had received DAAs without interferon."

Comment: I remain confused as to the meaning of "baseline". I appreciate that it is defined in the footnote of Table 1 as "Baseline was defined as latest of first prospective eGFR measurement, 1 January 2004, enrolment to EuroSIDA, known HCV antibody status and for those HCV antibody positive, known HCV-RNA status." I find this definition confusing. Can you help the reader better understand this? Why would baseline be so recent (e.g., after introduction of DAAs) when many participants have been screened for HCV and creatinine for years if not decades?

We have changed the description of baseline as per this reviewers request above, and it is copied to the footnote of Table 1 and Table 3 for consistency. As per the methods, enrolment

in EuroSIDA has been in waves with the most recent cohort added during 2014. All EuroSIDA analyses are left censored at inclusion into EuroSIDA to minimise survival bias, and this is why the baseline definition incorporates this date. We have not changed the manuscript further in response to this comment.

Author text: "Figure 1 shows the univariate and multivariate incidence rate ratios of CKD compared to those in group 4 (cured)."

Comment: The footnote of Figure 1 includes the following text "All factors are included at baseline with the exception of HCV group." It is unclear why information such as CD4 count is not time varying.

Please see our earlier response to this reviewer about model selection and the presentation of the 4 different models in the Table above.

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Influence of Hepatitis C (HCV) Co-Infection and HCV Treatment on Risk of Chronic Kidney Disease in HIV Positive Persons

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Abstract

Background: Hepatitis C virus (HCV) infection has been associated with increased risk of chronic kidney disease (CKD). We investigated the impact of HCV cure on CKD in HIV-positive persons in the EuroSIDA study.

Methods: HIV-positive persons with known HCV status and ≥3 serum creatinine measurements after 1/1/2004 were compared ~~included in five groups~~ based on time-updated HCV-RNA and HCV treatment: ~~1)~~ Anti-HCV negative, ~~2)~~ spontaneously cleared HCV, ~~3)~~ Chronic untreated HCV, ~~4)~~ Successfully treated HCV and ~~5)~~ HCV-RNA positive after HCV treatment. Poisson regression ~~was used to~~ compared incidence rates of CKD (confirmed [>3 months apart] eGFR < 60 ml/min/1.73m^2) between HCV strata~~groups~~.

Results: 14754 persons were included; at baseline 9273 (62.9%) were HCV-Ab negative, 696 (4.7%) spontaneous clearers, 3021 (20.5%) chronically infected, 922 (6.2%) successfully treated and 842 5.7%) HCV-RNA positive after treatment ~~5481 (37.1%) were HCV-positive at baseline~~. During 115335 person-years of follow-up (PYFU), 1128 (7.6%) developed CKD; crude incidence ~~rate~~ 9.8/1000 PYFU (95% CI 9.2–10.4). After adjustment, persons ~~in group 1 (~~Anti-HCV negative (~~;~~adjusted incidence rate ratio [aIRR] 0.59; 95% CI 0.46-0.75) and ~~group 2 (~~spontaneous clearers (~~;~~aIRR 0.67; 95% CI 0.47-0.97) had significantly lower rates of CKD compared to those cured ~~group 4 (successfully treated)~~ while persons ~~in group 3 (~~chronically infected (~~; a~~aIRR 0.85; 95% CI 0.65-1.12) and ~~group 5 (~~ HCV-RNA positive after treatment (~~;~~aIRR 0.71; 95% CI 0.49-1.04) had similar rates. Analysis in those without F3/F4 liver fibrosis and using a more rigorous definition of CKD showed similar results.

Conclusions: This large study found no evidence that successful HCV treatment reduced CKD ~~the~~ incidence ~~of CKD~~. Confounding by indication, where those with highest risk of CKD were prioritized for HCV treatment ~~, especially~~ in the DAA era, may contribute to these findings.

Introduction

Hepatitis C virus (HCV) coinfection has been implicated in a range of extra-hepatic diseases in HIV-positive persons including kidney disease~~,~~ [1-6]. ~~with only a few studies not reporting such an association~~. Some studies found those with chronic HCV infection had more ~~higher rates of~~ chronic kidney disease (CKD) compared with those with spontaneously cleared infection [1, 3] , while Butt et al found no difference comparing those with chronic and cleared infection [7]. Many of the earlier studies were limited by lack of data on HCV ~~-~~RNA and were therefore unable to distinguish between chronic untreated or spontaneously cleared HCV infection. The impact of HCV-related systemic inflammation and risk of ~~chronic kidney disease (~~CKD~~)~~ remains unclear, as highlighted in a recent review [8].

The introduction of direct acting antivirals (DAAs) for the treatment of HCV has had a major impact on HCV treatment [9] with cure rates in excess of 90% in persons coinfected with both HIV and HCV [10]. ~~Although c~~Case reports have shown that achievement of a sustained virological response (SVR) resulted in improvement in kidney function in persons with HCV-related glomerular nephritis [11]~~.~~ ~~,~~ Ceohort studies, including 100-350 persons with SVR and with no known underlying renal pathology, ~~where most of the patients have no known underlying renal pathology,~~ have been unable to document an improvement in kidney function in those with SVR compared with those treated for HCV without SVR [12-14]~~.~~ ~~.~~ One further study reported a ~~marginally significant~~ protective effect of SVR on CKD [15] which did not reach statistical significance and ~~, but~~ did not adjust for baseline renal function. Changes in renal function in these studies was measured in a variety of ways, and while slopes ~~declines~~ or rate of change in estimated glomerular filtration rate (eGFR) might be useful to study short term changes in renal function, a more rigorous definition of renal decline requiring confirmed low values over a period of 3 months, such as CKD [2], has greater clinical relevance given its association with other clinical events, including ~~such as~~ cardiovascular disease [16].

Given the lack of consensus from previous studies, methodological issues and the limited power and/or follow-up, we sought

~~The aim of this study was therefore~~ to investigate the incidence of CKD in a large pan-European multi-cohort study according to HCV status in HIV-coinfected persons across 5 groups ~~strata,~~ Anti-HCV negative, ~~anti-HCV negative~~, spontaneous HCV-RNA clearers, ~~with~~ chronic untreated HCV infection, cured HCV and HCV-RNA positive following ~~or failing~~ HCV treatment.

Methods

The EuroSIDA study

Persons were included from the EuroSIDA study, a large prospective observational cohort of almost 23000 HIV-1 positive patients followed in 100 hospitals in 35 European countries plus Israel and Argentina. Individuals were enrolled into ten cohorts from 1994 onward. In cohort ten all HIV positive patients were also required to be positive for anti-HCV antibodies (HCV-RNA positive, negative or unknown status). At recruitment, in addition to demographic and clinical data, a complete ART history was obtained together with the most recent CD4 cell counts and HIV-RNA measurements, as well as all HCV tests, HCV-RNA, HCV genotype, hepatitis B surface antigen (HBsAg) and HBV-DNA. Data is collected prospectively at clinical sites and sent to the coordinating centre at yearly intervals. At each follow-up visit, all CD4 cell counts, HIV-RNA, HCV tests, HCV-RNA, genotype, and HBsAg results measured since last follow-up are collected, together with start and stop dates for antiretroviral drugs and HCV and HBV drugs. Detailed information about data collected in EuroSIDA can be found at http://www.chip.dk/Ongoing-Studies/EuroSIDA/About.

Methods and definitions

CKD was defined as a confirmed (>3 months apart) eGFR < 60/ml/min/1.73m^2 for those with first eGFR > 60/ml/min/1.73m^2 and a confirmed (>3 months apart) 25% decline in eGFR for those with baseline eGFR ≤60/ml/min/1.73m^2. eGFRs were calculated using the CKD-EPI formula [17]. All persons with known HCV serostatus and prospective follow-up after 1 January 2004 (start of standardised collection of serum creatinine) were eligible for inclusion. Persons with <3 eGFRs during prospective follow-up were excluded, as were persons with less than 3 months follow-up. Baseline was defined as the first prospective visit in EuroSIDA after 1/1/2004 at which both eGFR and HCV serostatus were measured, and where HCV-RNA was known for those Anti-HCV positive. ~~latest of 1 January 2004, first eGFR, enrolment in EuroSIDA, known HCV serostatus and for those anti-HCV positive, known HCV-RNA status.~~ Persons aged < 16 at baseline or without a CD4 count and HIV viral load in the 12 months before or 1 month after baseline were excluded. ~~Persons were followed to the first of their last follow-up visit or CKD.~~

Based on time-updated HCV antibody tests, HCV-RNA and HCV treatment, we defined 5 HCV groups

1. Anti-HCV negative
2. HCV antibody positive, HCV-RNA negative, untreated (spontaneous clearers)
3. HCV antibody positive, HCV-RNA positive, untreated (chronic infections)

4. HCV antibody positive, HCV-RNA negative, treated (successfully treated with any HCV therapy; cured)
5. HCV antibody positive, HCV-RNA positive, treated (treated, HCV-RNA positive)

All groups Anti-HCV positive were defined on the basis of a single HCV-RNA measurement; for example, persons were classified as spontaneous clearers based on the latest value of HCV-RNA. ~~Note that g~~Group 5 (treated, HCV-~~-~~RNA positive) includes persons who did not achieve SVR, persons without an end of treatment response, persons who were HCV-RNA positive having started treatment more recently and those reinfected with HCV. Persons were followed until their last visit (median June 2018), date of death, or CKD, whichever occurred first. Person years of follow-up (PYFU) and CKD events accrued according to current HCV strata using the last observation carried forward and persons could contribute PYFU to multiple groups.

In those that developed CKD, we performed an exploratory analysis looking at ~~R~~reversal of CKD. This was ~~was~~ defined as a confirmed (> 3 months apart) increase in eGFR to > 60/ml/min/1.73m^2 among persons with at least 2 further eGFRs ~~after development of CKD~~ and ~~with~~ 3 months follow-up after CKD. Baseline for this analysis was date of developing CKD, and individuals were followed to the first of reversal of CKD or last eGFR.

Statistical Analysis

Characteristics of individuals ~~patients~~ were compared across strata using ~~simple summary statistics~~chi-squared statistics for categorical variables and the Kruskall-Wallis test for continuous variables. Incidence rates of CKD per 1000 person-years of follow-up (PYFU) were calculated within HCV groups, and Poisson regression was used to compare these rates with those cured ~~group 4 (cured)~~ as the reference group. Different models were investigated; the first adjusted only for the Data Collection on Adverse events of Anti-HIV Drugs~~D~~ (D:A:D) study CKD risk score [18], ~~and~~ without including the component due to HCV coinfection. L~~baseline~~iver fibrosis stage (as previously described; [19]; this was included as a baseline measurement ~~measured at baseline~~ as it may lie on the causal pathway between HCV status and CKD) and the HCV strata defined above were also included in this model. As the D:A:D CKD risk score does not include all the variables which differed between the HCV strata, we also investigated a more extensive model adjusting for many more potential confounding variables. Thise second model adjusted for ~~many~~ a greater number of potential confounding factors, all fixed at ~~at~~ baseline (gender, HIV exposure group, region of Europe Europe (North, Central West, South, Central East, East and Argentina [20]), eGFR, HIV viral load, prior AIDS, cardiovascular disease, non-AIDS defining malignancies (NADM), end stage liver disease (ESLD; ascites, hepatorenal syndrome, grade III/IV hepatic encephalopathy, unspecified liver decompensation, oesophageal variceal bleeding, spontaneous bacterial peritonitis, liver transplantation and hepatocellular carcinoma)~~;~~ ~~f~~Further information about these events is available at https://www.chip.dk/Studies/EuroSIDA/Study-documents). We also adjusted for~~,~~ smoking status (never smoked, current smoker, past smoker, unknown smoking status), hypertension, body mass index (BMI), use of nephrotoxic ARVs (tenofovir, atazanavir [unboosted and/or ritonavir boosted], indinavir, and lopinavir), use of nephrotoxic drugs (foscarnet, acyclovir, pentamidine, cidofovir, amphotericin B), CD4, nadir CD4, age, liver fibrosis and baseline date. A third model adjusted for baseline liver fibrosis and the components of the D:A:D CKD risk score (including use of nephrotoxic ARVs and HCV status as defined in this study) at baseline as separate variables rather than a composite score. The model was additionally ~~This model also~~ adjusted for starting integrase inhibitors, shown to increase serum creatinine levels [21], as a time updated variable. As results were consistent across models, our results focus on model 3 which had the lowest Akaike Information Criterion.

We performed a wide range of sensitivity analyses to investigate the robustness of our results to different assumptions. We performed a sensitivity analysies where the last HCV~~-~~-RNA measurement was carried forward for a maximum of 12 months. This reduces the bias from HCV-RNA

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measurements measured many years previously being used to stratify persons into HCV strata. We also ~~,~~ exclud~~ed~~ed~~ing~~ persons with stage F3/F4 liver fibrosis at baseline, as well as ~~excluding all follow-up~~PYFU and CKD events occurring after the development of F3/F4 liver fibrosis ~~during follow-up,~~ in the subgroup of persons at high risk for CKD using the D:A:D CKD risk score[18], and an analysis limited to after 2014, when DAAs became more widely available for persons included in the EuroSIDA study [22]. We also explored a more rigorous~~n alternative~~ definition of CKD as a confirmed 25% decline to <60/ml/min/1.73m^2 [1]~~.~~. We repeated our analyses ~~additionally performed exploratory analyses~~separately among those treated and cured or HCV-RNA positive after treatment ~~where group 4 (cured) and group 5 (treated; HCV-RNA positive) were limited to~~ in those not exposed, or only exposed, to DAA-based regimens.

All analyses were performed in SAS version 9.4 (Statistical Analysis Software, Cary NC, USA).

Results

Of 22826 persons enrolled in EuroSIDA, 6806 were excluded due to unknown HCV status, insufficient follow-up or with CKD before baseline. An additional 1266 persons were excluded with unknown HCV -RNA status for those who were anti-HCV positive, or with missing baseline CD4 counts and viral load. Compared to the 14754 included, the 1266 excluded were less likely to be MSM, were less likely to be from Central, or West Europe and more likely to be from Central East, Eastern Europe or Argentina compared to southern Europe. They were also less likely to have suppressed HIV viral load and more likely to have a prior AIDS diagnosis (all p<0.05).

Table 1 shows the characteristics of the 14754 included persons, stratified by baseline HCV strata. The 5 HCV strata were quite heterogenous and there were many significant differences across the groups (see footnote to Table 1). As would be expected, the proportion of injecting drug uses (IDUs) was lowest in those group 1 (Anti-HCV negative), the proportion with prior ESLD (only 3 persons had a prior diagnosis of hepatorenal syndrome) was highest in those group 5 (treated; HCV-RNA positive after treatment) and the burden from F3/F4 liver fibrosis was highest in both those cured and HCV-RNA positive after treatmente HCV treated groups (group 4/5), as was . Tthe proportion who had received tenofovir disoproxil fumaerate (TDF)TDF at baseline was also highest in group 4 (cured) and group 5 (treated; HCV-RNA positive). The median age was 43 years (interquartile range [IQR] 37 - 51), baseline CD4 cell count was 470/mm^3 (IQR 318–669) and CD4 nadir 174/mm^3 (IQR 70–281). 1764 persons had been previously treated for HCV; the majority of these (1467; 83.2%) had been treated with interferon plus ribavirin. At baseline, 181 had received a DAA plus interferon, and 275 had received DAAs without interferon.

The analysis included 280,022 eGFRs with a median of 16 (IQR 8–28) per person and 2.4 (IQR 1.9–3.0) per year of follow-up. The number of measures per person per year were similar across the 5 HCV strata, ranging from 2.2/year (IQR 1.7–3.0) in group 2 (spontaneous clearers) to 2.4/year in those Anti-HCV groups 1 (HCV negative), those cured and those group 4 (cured) and group 5 (treated; HCV-RNA positive after treatment). The median eGFR at baseline was 99 ml/min/1.73m^2 (IQR 85- 110). 4420 (30.0%) were at low risk of CKD using the D:A:D risk score, 5089 (34.5%) were at medium risk and 5243 (35.5%) were at high risk, with significant differences between HCV strata. At baseline, 2842 of those in group 1 (Anti-HCV negative; 30.6%) were at high risk (30.6%), increasing to 545 of those in group 4 (cured; (59.1%) and 425 in group 5 (treated; in those HCV-RNA positive after treatment (; 50.5%).

The incidence of CKD in HCV strata

During 115,335 ~~person-years of follow-up (~~PYFU~~)~~; a median 7.0 (IQR 3.7–12.4) per person, 1130 (7.7%) developed CKD; the crude incidence rate per 1,000 person-years of follow-up was 9.8 (95% confidence interval [CI] 9.2–10.4). Table 2 shows the crude incidence rate in each of the HCV strata. The incidence rate was lowest in those ~~group 5 (treated;~~ HCV-RNA positive following treatment; incidence rate 7.7/1000 PYFU; 95% CI 5.2–10.1) and highest in those cured ~~group 4 (cured);~~ 12.9/1000 PYFU (95% CI 10.4–15.3). Figure 1 shows the univariate and multivariate incidence rate ratios of CKD compared to those ~~in group 4 (~~cured~~)~~. After adjustment (model 3, adjusting separately for the components of the D:A:D CKD risk score, liver fibrosis stage at baseline and use of integrase inhibitors those ~~in group 1 (~~Anti-HCV negative ~~(;~~ adjusted incidence rate ratio [aIRR] 0.50; 95% CI 0.39–0.63) and ~~group 2 (~~spontaneous clearers ~~(;~~ aIRR 0.67; 95% CI 0.47-0.97) had significantly lower rates of CKD compared to those cured~~group 4 (cured)~~. Those chronically infected ~~in group 3 (chronic infections; (~~aIRR 0.85; 95% CI 0.65-1.12) and ~~group 5 (treated;~~ HCV-RNA positive after treatment ~~(;~~ aIRR 0.71; 95% CI 0.49-1.04) had non-significant reduced rates of CKD compared to those ~~group 4 (~~cured~~)~~.

The proportion of follow-up time with eGFR > 90 ml/min/1.73m^2 was 62.5%, and was highest in those with ~~group 3 (~~chronic infections ~~(,~~ 69.2%) and lowest in those cured ~~group 4 (cured, (~~55.0%). Of 1128 who developed CKD, 926 (82.1%) had at least 2 further eGFRs and 3 months follow-up. Of these 926, 442 (47.7%) had a reversal of CKD during subsequent follow-up. By 12 months after CKD, 17.2% were estimated to have reversed CKD (95% CI 14.7–19.7) from Kaplan-Meier estimates, with no differences between the HCV strata at development of CKD (p=0.56). The proportion who reversed CKD was lowest overall for those cured ~~group 4 (cured; (~~23/72, 31.9%) and highest for those chronically infected ~~group 3 (chronic infections; (~~53/102, 52.0%), but this was not statistically significant (p=0.083). The median eGFR at CKD was 53.4 (IQR 47.2–57.0 ml/min/1.73m^2) and was lowest in those chronically infected ~~group 3 (chronic infections; (~~median 50.4, IQR 44.2–56.3 ml/min/1.73m^2), and highest in those ~~group 1 (~~anti-HCV negative ~~(,~~ median 53.6, IQR 48.2–57.0 ml/min/1.73m^2). ~~There were few differences between group 1 (anti-HCV negative), group 2 (spontaneous clearers), group 4 (cured) and group 5 (treated; HCV-RNA positive).~~

Sensitivity analyses

The results from a wide range of sensitivity analyses showed similar results. Of note, an analysis excluding those with F3/F4 or unknown liver fibrosis at baseline included 442 events during 52085 PYFU (incidence of CKD 8.5/1000 PYFU; 95% CI 7.7–9.3) and showed similar results; albeit with wider confidence intervals. In this analysis, those ~~in group 1 (~~anti-HCV negative~~)~~ had significantly reduced rates of CKD (aIRR 0.65; 95% CI 0.47–0.89) compared to those ~~group 4 (~~cured~~; adjusted incidence~~

~~rate ratio [aIRR] 0.65; 95% CI 0.47–0.89),~~ with no significant differences between other groups (left hand side; Figure 2).

Our results were also consistent when we investigated separately HCV treatments including interferon or DAAs in those treated and cured or HCV-RNA positive after treatment, with limited power in the latter analysis. ~~Excluding all events and PYFU among those treated with DAA in group 4 (cured) and 5 (treated, HCV-RNA positive) also showed similar results to our main analysis.~~ There were 1068 events during 111,228 PYFU when DAA treatments were excluded from those cured or HCV-RNA positive after treatment ~~in this analysis,~~ with an overall incidence rate of 9.6 (9.0–10.3), and the results are shown in the middle panel of Figure 2. ~~–~~ Similarly, when only including DAA treatments in those cured or HCV-RNA positive after treatment, there were 1036 events during 105,291 PYFU, and the results are shown on the right hand side of figure 2. In this analysis, those Anti-HCV negative had significantly lower rates of CKD and those with spontaneous clearance had marginally lower rates of CKD compared to those cured.

Having a more stringent definition for CKD of a confirmed 25% decline in eGFR to <60 ml/min/1.73m^2 resulted in a lower incidence of CKD (1001 events during 116369 PYFU, rate 8.6/1000 PYFU; 95% CI 8.1–9.1), but also showed a lower incidence of CKD in ~~group 1 (~~those anti-HCV negative), consistent with our main findings. ~~(Figure 2, right hand side).~~

Characteristics of HCV treated persons at CKD or last visit

Our final analysis focused further on those treated for HCV~~in group 4 and 5~~. Characteristics of persons at CKD or last visit for those not developing CKD are shown in Table 3. Of note, there was a much higher proportion of persons with ESLD in those cured who developed CKD, likely reflecting targeted treatment to those with most advanced liver disease when DAAs first became available. ~~There was a larger proportion with ESLD in those with CKD in those group 4 (cured) compared to those without CKD in group 4 (cured) or either those with or without CKD in group 5 (treated; HCV-RNA positive). In those with CKD in both groups 4 (cured) and group 5 (treated; HCV-RNA positive) there was a higher proportion of persons treated with interferon plus ribavirin and a lower proportion treated with DAA only therapy compared to those who did not develop CKD in either group~~in both those cured or HCV-RNA positive after ~~treatment.~~ ~~–~~ As would be expected, those cured had a much higher proportion of people who had received DAA treatment compared to those HCV-RNA positive after treatment, regardless of whether they developed CKD or not.

Discussion

This large study of almost 15,000 individuals with a median follow-up of approaching 7 years and with known anti-HCV and HCV RNA status has found no reduction in CKD among those with cured HCV infection following treatment for HCV~~; those in group 4 (cured) had the highest rates of CKD compared to other HCV strata.~~ To date, this is the largest study focused on CKD in HIV and HCV co-infected individuals comparing across HCV strata.

As previously reported by EuroSIDA and others [1, 3, 23], we found the lowest rates of CKD in those who were anti-HCV negative ~~(group 1)~~ or those with spontaneous clearance of HCV RNA ~~(group 2),~~ as well as traditional factors associated with CKD, including age, hypertension, diabetes and the use of potentially nephrotoxic ARVS, as reported by many previous studies [24-26]. Cure of HCV with treatment has a number of benefits, including a reduction on both all cause and liver related mortality[27]. We were not able to demonstrate that HCV cure resulted in lower rates of CKD, consistent with ~~most~~ previous studies[12-14] which had smaller populations and less power, or which considered decline in eGFR rather than ~~a more rigourous endpoint of~~ CKD. ~~. Importantly, our s~~Our study ~~tudy~~ defined CKD rigorously using a confirmed eGFR < 60 ml/min/1.73m^2 over a period of 3 months. Slopes or rate of change in ~~and did not consider changes in~~ eGFR ~~which~~ is ~~are~~ arguably less clinically relevant than ~~our~~the definition used here. Our study was also able to ~~, and~~ adjust~~ed~~ for a number of important confounding variables. HIV-associated nephropathy, membranous nephropathy and membranoproliferative glomerulonephritis are sometimes found at biopsy in HIV and HCV coinfected persons [28-30] and more studies on the role of HIV-infection, HCV coinfection, HCV RNA and cure of HCV RNA on these pathologies is warranted. The role of HCV in extrahepatic comorbidities is not fully understood, but may be related to the direct effect of HCV, immune activation or indirect effects such as drug and alcohol use [27].

In the pre-DAA era, there was some evidence in HCV monoinfected persons that interferon-based HCV treatment improved renal function and decreased the risk of CKD [31-33]. More recently, a study from Taiwan in monoinfected persons suggested a small decrease in renal function in persons treated with DAAs, although the changes were thought to be clinically insignificant [34]. The results from previous studies are difficult to compare to our findings. Although some were large studies, not all had information on HCV treatment outcomes, baseline eGFR, pre-dated the introduction of DAAs or included specific subgroups, such as those with cirrhosis. In addition, the contribution of different factors in coinfected individuals, including lifestyle factors, socioeconomic status and mechanisms other than HCV replication, may play a role in the development of CKD [35-37].

We found the highest rates of CKD in those cured, although they were not significantly higher than those with chronic hepatitis C or those who were HCV-RNA positive following HCV treatment. There are several possible reasons for our findings. Our study includes coinfected persons and follow-up to the middle of 2018. DAA treatment in EuroSIDA began to increase most notably around 2015 [22]; prior to this it is likely that the healthiest persons were selected for interferon treatment. Following 2015, those with F3/F4 liver fibrosis and more advanced liver disease were prioritized for DAA treatment. Those ~~in group 4 (~~cured~~)~~ were also less likely to reverse their CKD and the proportion of follow-up with an eGFR > 90 ml/min/1.73m^2 was lowest, possibly suggesting a higher risk for renal disease. More of those ~~in group 4 (~~cured~~)~~ developing CKD had a prior diagnosis of ESLD and those developing CKD in both those treated and cured and ~~groups 4 (cured) and 5 (treated;~~ HCV-RNA positive following treatment ~~)~~ were more likely to have been treated with interferon plus ribavirin. While we have adjusted for a wide range of confounders, it is possible that our findings reflect confounding by indication and further follow-up of persons treated with new generation DAAs is warranted.

Our study has a number of limitations. First and foremost, our data are from a cohort study and while we have defined 5 distinct HCV strata based on single values of Anti-HCV tests and HCV-RNA, comparisons across these strata are limited by our ability to adjust for differences as well as the possibility of unknown or unmeasured confounding that we cannot adjust for. We were not able to adjust for duration of HCV infection which may be an important confounder. As in a previous study [38], we chose not to define SVR according to treatment guidelines [21] in part due to differences between the many centres in EuroSIDA in frequency of HCV-RNA monitoring following treatment. We used the last HCV -RNA carried forward and where this was negative after HCV treatment assumed SVR ~~(group 4,~~ or cure). Similarly, for persons ~~group 5 (treated;~~ HCV-RNA positive after treatment~~)~~, the individual may have only recently started treatment and with additional follow-up may be cured and move into this stratum~~a~~ ~~group 4~~. EuroSIDA has not routinely collected information on proteinuria and we may be underestimating the incidence of CKD by not having this data for the majority of participants. DAA regimens including sofosbuvir/ledipasvir and sofosbuvir/velpatasvir have been shown to increase the plasma concentration of tenofovir, especially when used with a boosted protease inhibitor [39], but we were not able to investigate an interaction between DAAs and tenofovir due to limited power. The strength of our study is that it is one of the largest of coinfected persons reported to date, with an extensive quality assurance and data monitoring program.

Although HCV-RNA positive persons have previously been shown to have higher rates of CKD, curing HCV with HCV treatment was not associated with a lower rate of CKD in this study. Further long term follow-up is required to investigate the role of DAAs as their use becomes widespread to determine if the higher rates seen in this study were due to underlying high risk of CKD and new DAAs being targeted at the sickest individuals.

Table 1 Characteristics at baseline

		All		Anti-HCV negative Group 1		HCV antibody positive							
						Group 2 Spontaneous clearers		Group 3 Chronic untreated infection		Group 4 Cured		Group 5 treated; HCV-RNA positive	
		N	%	N	%	N	%	N	%	N	%	N	%
All		14754	100.0	9273	62.9	696	4.7	3021	20.5	922	6.2	842	5.7
Gender	M	10917	74.0	7023	75.7	454	65.2	2125	70.3	694	75.3	621	73.8
	F	3837	26.0	2250	24.3	242	34.8	896	29.7	228	24.7	221	26.2
HIV risk	MSM	5762	39.1	4856	52.4	103	14.8	393	13.0	241	26.1	169	20.1
	IDU	3588	24.3	245	2.6	391	56.2	1974	65.3	485	52.6	493	58.6
	Het	4300	29.1	3503	37.8	128	18.4	437	14.5	118	12.8	114	13.5
	Other	1104	7.5	669	7.2	74	10.6	217	7.2	78	8.5	66	7.8
Ethnic	White	12562	85.1	7776	83.9	565	81.2	2763	91.5	745	80.8	713	84.7
Origin	Other	2192	14.9	1497	16.1	131	18.8	258	8.5	177	19.2	129	15.3
Region	South	3773	25.6	2094	22.6	161	23.1	880	29.1	299	32.4	339	40.3
	Central	3939	26.7	2594	28.0	234	33.6	534	17.7	340	36.9	237	28.1
	North	3186	21.6	2332	25.1	127	18.2	483	16.0	136	14.8	108	12.8
	Central East	2041	13.8	1273	13.7	85	12.2	543	18.0	59	6.4	81	9.6
	East	1407	9.5	632	6.8	83	11.9	536	17.7	84	9.1	72	8.6
	Argentina	408	2.8	348	3.8	6	0.9	45	1.5	4	0.4	5	0.6
HBV status	Negative	12631	85.6	8218	88.6	524	75.3	2430	80.4	772	83.7	687	81.6
	Positive	1128	7.6	690	7.4	119	17.1	207	6.9	61	6.6	51	6.1
	Unknown	995	6.7	365	3.9	53	7.6	384	12.7	89	9.7	104	12.4
Ever cART	No	1703	11.5	1171	12.6	55	7.9	309	10.2	87	9.4	81	9.6
	Yes	13051	88.5	8102	87.4	641	92.1	2712	89.8	835	90.6	761	90.4
HIV VL	<500	11165	75.7	6801	73.3	563	80.9	2277	75.4	813	88.2	711	84.4
	>500	3589	24.3	2472	26.7	133	19.1	744	24.6	109	11.8	131	15.6
Comorbidities	AIDS	3838	26.0	2541	27.4	189	27.2	771	25.5	159	17.2	178	21.1
	CVD	410	2.8	282	3.0	23	3.3	56	1.9	32	3.5	17	2.0
	NADM	337	2.3	201	2.2	23	3.3	64	2.1	29	3.1	20	2.4
	ESLD	203	1.4	50	0.5	12	1.7	75	2.5	31	3.4	35	4.2
	Hypertension	3969	26.9	2689	29.0	178	25.6	630	20.9	253	27.4	219	26.0
	Diabetes	743	5.0	486	5.2	35	5.0	107	3.5	56	6.1	59	7.0

Table 1 Characteristics at baseline (ctd)

		All		Anti-HCV negative Group 1		HCV antibody positive Group 2 Spontaneous clearers		Group 3 Chronic untreated infection		Group 4 Cured		Group 5 treated; HCV-RNA positive	
		N	%	N	%	N	%	N	%	N	%	N	%
All		14754	100.0	9273	62.9	696	4.7	3021	100	922	100	842	100
Smoking status	Never	4299	29.1	3478	37.5	103	14.8	403	13.3	164	17.8	151	17.9
	Current	7380	50.0	3949	42.6	444	63.8	2047	67.8	472	51.2	468	55.6
	Previous	1896	12.9	1241	13.4	93	13.4	322	10.7	127	13.8	113	13.4
	Unknown	1179	8.0	605	6.5	56	8.0	249	8.2	159	17.2	110	13.1
~~Fibrosis~~Liver Fibrosis	0/1	7270	49.3	4025	43.4	475	68.2	1751	58.0	576	62.5	443	52.6
	2	492	3.3	37	0.4	23	3.3	206	6.8	110	11.9	116	13.8
	3	245	1.7	16	0.2	6	0.9	96	3.2	67	7.3	60	7.1
	4	484	3.3	44	0.5	26	3.7	197	6.5	96	10.4	121	14.4
	Unknown	6263	42.4	5151	55.5	166	23.9	771	25.5	73	7.9	102	12.1
D:A:D CKD score	Low	4422	30.0	3532	38.1	99	14.2	605	20.0	98	10.6	88	10.5
	Medium	5089	34.5	2899	31.3	294	42.2	1288	42.6	279	30.3	329	39.1
	High	5243	35.5	2842	30.6	303	43.5	1128	37.3	545	59.1	425	50.5
Prior HCV Treatment*	IFN + RBV	1441	81.7							724	78.5	717	85.2
	DAA + IFN	181	10.3							117	12.7	64	7.6
	DAA only	275	15.6							186	20.2	89	10.6
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age	years	43	37–51	43	36–51	44	38–51	41	35–47	48	41–53	46	40–52
CD4	/mm^3	470	318–669	461	320–653	484	344–714	440	282–643	558	376–782	543	370–741
Nadir CD4	/mm^3	174	70–281	176	70–283	163	57–280	164	71–273	182	79–286	190	99–282
Baseline	Mm/yy	10/06	7/04–6/12	11/05	6/04–11/08	10/12	1/05–2/15	02/10	12/04–11/14	11/14	7/14–6/15	10/14	7/08–5/15

Baseline was defined as the first prospective visit in EuroSIDA after 1/1/2004 at which both eGFR and HCV serostatus were measured, and where HCV-RNA was known for those Anti-HCV positive . ~~Baseline was defined as latest of first prospective eGFR measurement, 1 January 2004, enrolment to EuroSIDA, known HCV antibody status and for those HCV antibody positive, known HCV-RNA status.~~ Spontaneous clearers (HCV antibody positive, HCV-RNA negative, untreated); chronic untreated infection (HCV antibody positive, HCV-RNA positive, untreated); cured (HCV antibody positive, HCV-RNA negative, treated); treated, HCV-RNA positive (HCV antibody positive, HCV-RNA positive, treated). IFN; interferon. RBV; ribavirin. DAA; direct acting antivirals. ~~All p<0.0001 except prior NADM (p=0.12), prior CVD (p=0.0029), nadir CD4 (p=0.0051), and HCV treatment with DAA+IFN (p=0.0004).~~ *45 persons had previously been exposed to both IFN+RBV and DAA+IFN~~NF~~, 81 to both IFN~~NF~~+RBA and DAA only, 11 to DAA+IFN~~NF~~ and DAA only, and 11 to IFN~~FN~~+RBV, DAA+INF and DAA only. All p<0.0001 except prior NADM (p=0.12), prior CVD (p=0.0029), nadir CD4 (p=0.0051), and HCV treatment with DAA+IFN~~FN~~ (p=0.0004). Characteristics of individuals ~~were~~ compared across strata using chi-squared statistics for categorical variables and the Kruskall-Wallis test for continuous variables

Table 2 Crude incidence rates of CKD stratified by current HCV strata

		HCV ab status	HCV--RNA	HCV treatment	Events	PYFU	Rate / 1000 PYFU	95% CI
Total					1128	115335	9.8	9.2–10.4
Group 1	Anti-HCV negative	Negative	n/a	n/a	814	82523	9.9	9.2–10.5
Group 2	Spontaneous clearers	Positive	Negative	Untreated	42	4854	8.7	6.0–11.3
Group 3	Chronically infected	Positive	Positive	Untreated	125	14516	8.6	7.1–10.1
Group 4	Successfully treated	Positive	Negative	Treated	109	8479	12.9	10.4–15.3
Group 5	treated; HCV-RNA positive	Positive	Positive	Treated	38	4963	7.7	5.2–10.1

PYFU; person years of follow-up. CI confidence interval

Table 3 Characteristics at CKD or last visit in group 4 (cured) and group 5 (treated; HCV-RNA positive)

		All		Group 4; cured				Group 5; treated; HCV-RNA positive			
				No CKD		CKD		No CKD		CKD	
		N	%	N	%	N	%	N	%	N	%
All		3231	100	2553	79.0	109	3.4	531	16.4	38	1.2
Gender	M	2415	74.7	1929	75.6	76	69.7	387	72.9	23	60.5
	F	816	25.3	624	24.4	33	30.3	144	27.1	15	39.5
HIV risk	MSM	716	22.2	596	23.3	23	21.1	90	16.9	7	18.4
	IDU	1819	56.3	1413	55.3	62	56.9	320	60.3	24	63.2
	Het	444	13.7	349	13.7	13	11.9	78	14.7	4	10.5
	Other	252	7.8	195	7.6	11	10.1	43	8.1	3	7.9
HBV status	Negative	2672	82.7	2102	82.3	93	85.3	447	84.2	30	78.9
	Positive	208	6.4	169	6.6	9	8.3	26	4.9	4	10.5
	Unknown	351	10.9	282	11.0	7	6.4	58	10.9	4	10.5
HIV VL	<500 copies/ml	3116	96.4	2486	97.4	106	97.2	488	91.9	36	94.7
Comorbidies	ESLD	104	3.2	76	3.0	12	11.0	15	2.8	1	2.6
Liver~~Fibrosis~~	0/1	2018	62.5	1592	62.4	67	61.5	331	62.3	28	73.7
Fibrosis	2	451	14.0	363	14.2	10	9.2	75	14.1	3	7.9
	3	289	8.9	234	9.2	9	8.3	42	7.9	4	10.5
	4	446	13.8	346	13.6	19	17.4	78	14.7	3	7.9
	Unknown	27	0.8	18	0.7	4	3.7	5	0.9	0	0.0
Prior HCV	IFN + RBV	1393	43.1	959	37.6	56	51.4	347	65.3	31	81.6
Treatment	DAA + IFN	189	5.8	168	6.6	4	3.7	16	3.0	1	2.6
	DAA only	1649	51.0	1426	55.9	49	45.0	168	31.6	6	15.8
	SOF/RBV	85	5.2	80	5.6	2	4.1	3	1.8	0	0.0
	SOF/DCV	241	14.6	206	14.4	14	28.6	20	11.9	1	16.7
	SOF/SMV	51	3.1	47	3.3	3	6.1	1	0.6	0	0.0
	SOF/LDV	678	41.1	595	41.7	14	28.6	67	39.9	2	33.3
	OBV/PTV	56	3.4	52	3.6	0	0.0	4	2.4	0	0.0
	OBV/PTV/DSV	167	10.1	146	10.2	6	12.2	14	8.3	1	16.7
	GZR/EBR	151	9.2	128	9.0	5	10.2	17	10.1	1	16.7
	SOF/VEL	141	8.6	105	7.4	4	8.2	31	18.5	1	16.7
	GLE/PIB	56	3.4	46	3.2	0	0.0	10	6.0	0	0.0
	Other	23	1.4	21	1.5	1	2.0	1	0.6	0	0.0

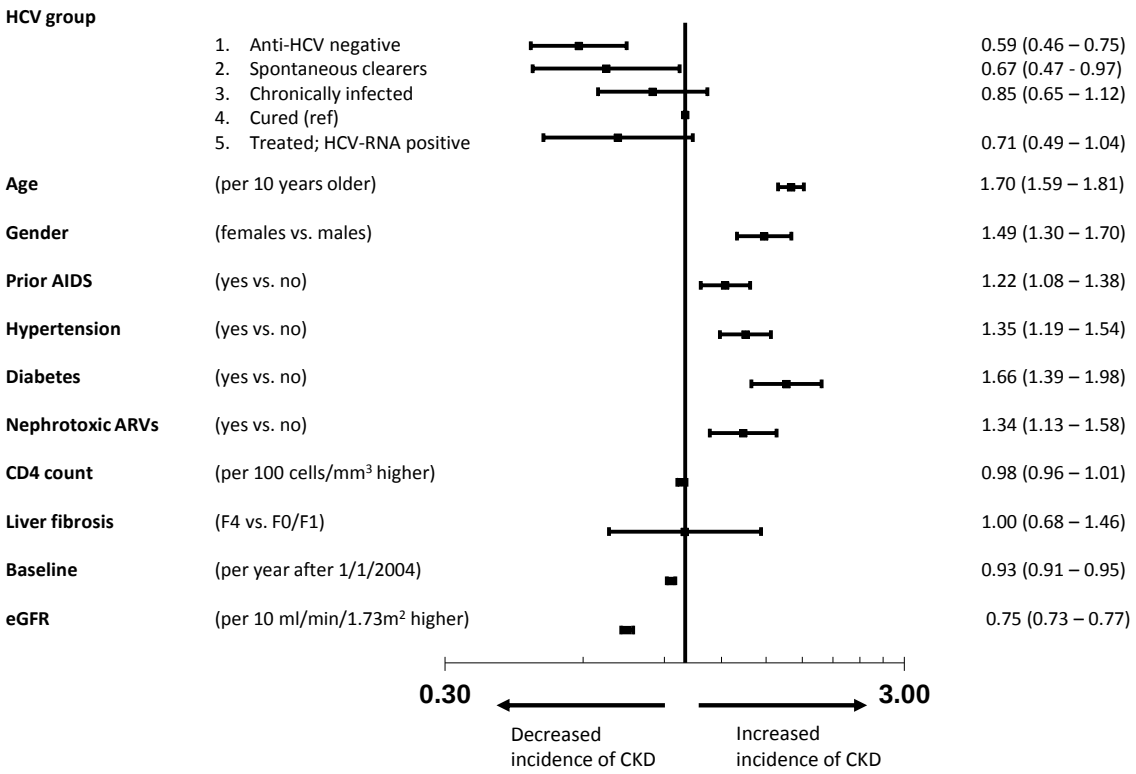
~~SOF; sofosbuvir. DCV; daclatasvir. SMV; simeprevir. LDV; ledipasvir. OBV; ombitasvir; PTV; paritaprevir. DSV; dasabuvir. GZR; grazoprevir. EBR; elbasvir. VEL; velpatasvir; GLE; glecaprevir. PIB; pibrentasvir~~

Table 3 Characteristics at CKD or last visit in group 4 (cured) and group 5 (treated; HCV-RNA positive) ctd

		All		Group 4; cured				Group 5; treated; HCV-RNA positive			
				No CKD		CKD		No CKD		CKD	
		N	%	N	%	N	%	N	%	N	%
All		3231	100	2553	79.0	109	3.4	531	16.4	38	1.2
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age	years	52	45–57	52	45–57	54	50–58	49	42–54	52	47–59
CD4	/mm^3	614	444–628	628	460–853	600	442–830	560	399–785	481	390–818
Baseline	Mm/yy	09/14	04/06–04/15	10/14	06/08–05/15	02/14	09/04–12/14	12/10	11/04–12/14	07/04	04/04–12/14
Nadir CD4	/mm^3	180	80–283	180	81–285	148	60–260	180	84–281	144	60–214
Yrs since first HCV treatment started		5.6	2.6–10.3	5.6	2.6–10.4	5.6	1.9–10.2	5.8	2.3–10.1	7.8	4.3–10.0
Months since last HCV treatment started		3.4	1.8–7.0	3.3	1.8–6.6	3.1	1.5–7.8	4.5	1.4–8.6	5.5	2.2–8.6

Baseline was defined as the first prospective visit in EuroSIDA after 1/1/2004 at which both eGFR and HCV serostatus were measured, and where HCV-RNA was known for those Anti-HCV positive~~Baseline was defined as latest of first prospective eGFR measurement, 1 January 2004, enrolment to EuroSIDA, known HCV antibody status and for those HCV antibody positive, known HCV RNA status~~. INF; interferon. RBV; ribavirin. DAA; direct acting antivirals. SOF; sofosbuvir. DCV; daclatasvir. SMV; simeprevir. LDV; ledipasvir. OBV; ombitasvir; PTV; paritaprevir. DSV; dasabuvir. GZR; grazoprevir. EBR; elbasvir. VEL; velpatasvir; GLE; glecaprevir. PIB; pibrentasvir

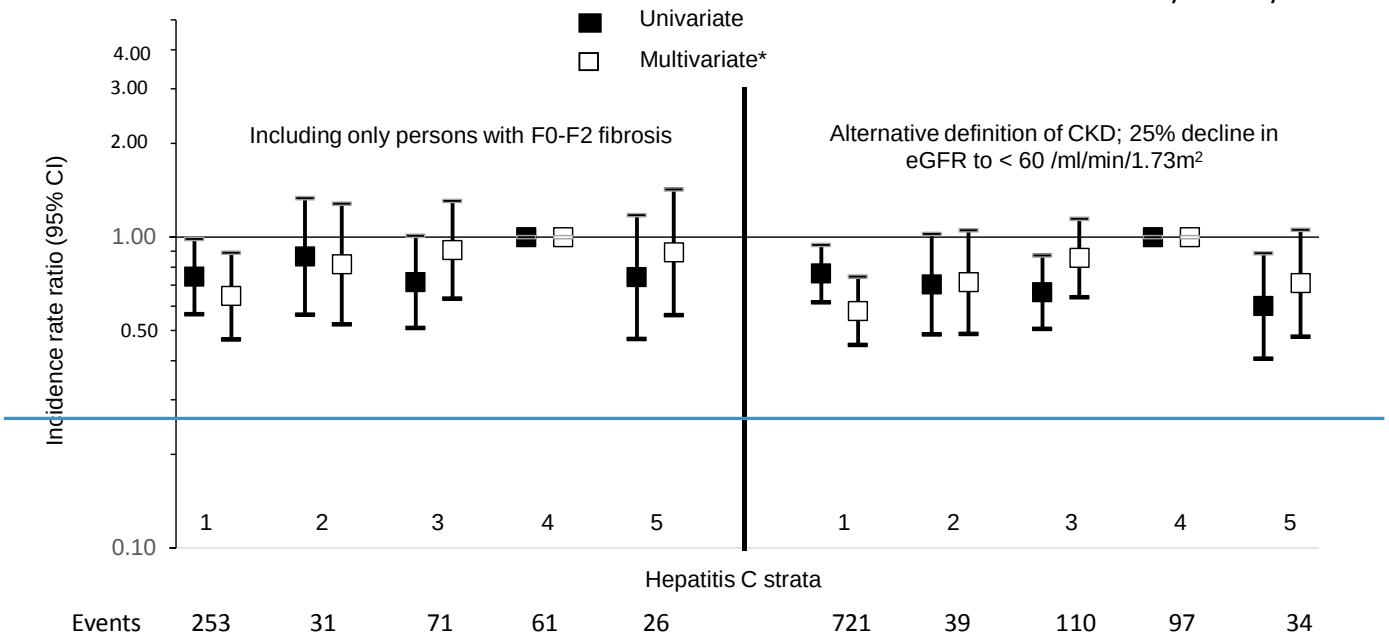
Figure 1
Multivariate incidence rate ratios of CKD



All factors are included at baseline with the exception of HCV group. *Model additionally adjusted for starting integrase inhibitors as a time-updated variable

Figure 2

Univariate and multivariate* incidence rate ratios of CKD: Sensitivity analyses

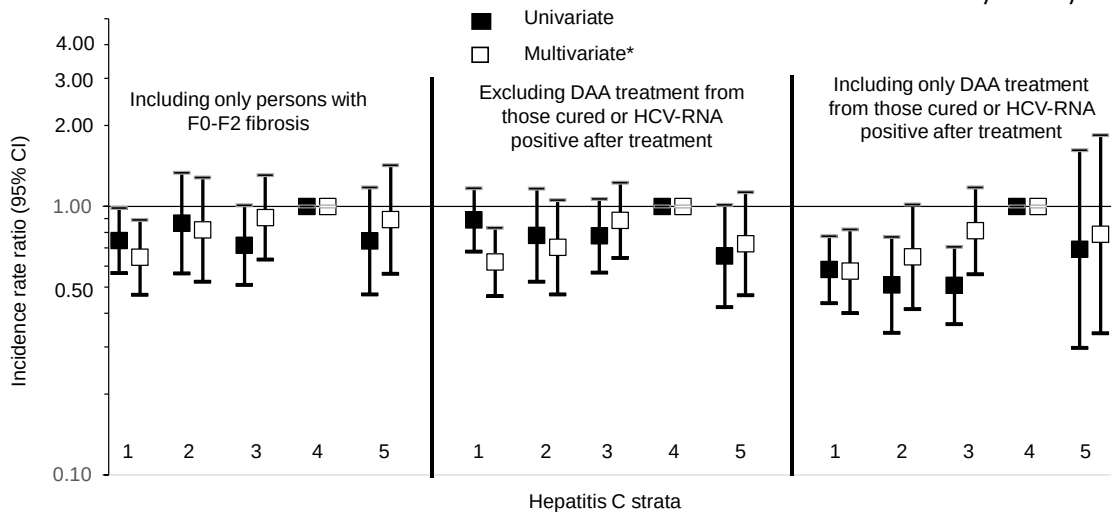


HCV status	*HCV RNA*	*HCV treatment*		*Group*
Negative	Negative	N/A	Anti-HCV negative	1
Positive	Negative	Untreated	Spontaneous clearers	2
Positive	Positive	Untreated	Chronic infection	3
Positive	Negative	Treated	Cured	4
Positive	Positive	Treated	Treated; HCV-RNA positive	5

*Adjusted for eGFR, use of nephrotoxic ARV, AIDS, hypertension, diabetes, baseline CD4, age, fibrosis stage and baseline date, all at baseline and starting integrase inhibitors as a time-updated variable

Figure 2

Univariate and multivariate* incidence rate ratios of CKD: Sensitivity analyses



HCV status	*HCV RNA*	*HCV treatment*		*Group*
Negative	Negative	N/A	Anti-HCV negative	1
Positive	Negative	Untreated	Spontaneous clearers	2
Positive	Positive	Untreated	Chronic infection	3
Positive	Negative	Treated	Cured	4
Positive	Positive	Treated	Treated; HCV-RNA positive	5

*Adjusted for eGFR, use of nephrotoxic ARV, AIDS, hypertension, diabetes, baseline CD4, age, liver fibrosis stage and baseline date, all at baseline and starting integrase inhibitors as a time-updated variable

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Appendix

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The Editors, AIDS

10 March 2020

Dear Sirs,

Influence of Hepatitis C (HCV) Co-Infection and HCV Treatment on Risk of Chronic Kidney Disease in HIV Positive Persons : AIDS-D-20-00052

Many thanks for the careful review of the manuscript from the reviewers. We have attached separately a detailed response to the reviewers. Reviewer 1 was particularly negative about our work and the role of cohort studies, and we have tried to address all their concerns but unfortunately we are not able to change the study design or the fact that we are analysing data from a cohort study.

We have attached a track changes as well as a clean version of the revised manuscript, and hope that you agree that this manuscript is now suitable for publication in AIDS. Please do not hesitate to contact me if there is any additional information you require at this stage.

Yours faithfully

Amanda Mocroft PhD, on behalf of the EuroSIDA study group

Professor of Epidemiology and Medical Statistics