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	Never	4299	29.1	3478	37.5	103	14.8	403	13.3	164	17.8	151	17.9
status	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	0/1	7270	49.3	4025	43.4	475	68.2	1751	58.0	576	62.5	443	52.6
Fibrosis	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	Low	4422	30.0	3532	38.1	99	14.2	605	20.0	98	10.6	88	10.5
score	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	IFN + RBV	1441	81.7							724	78.5	717	85.2
Treatment*	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

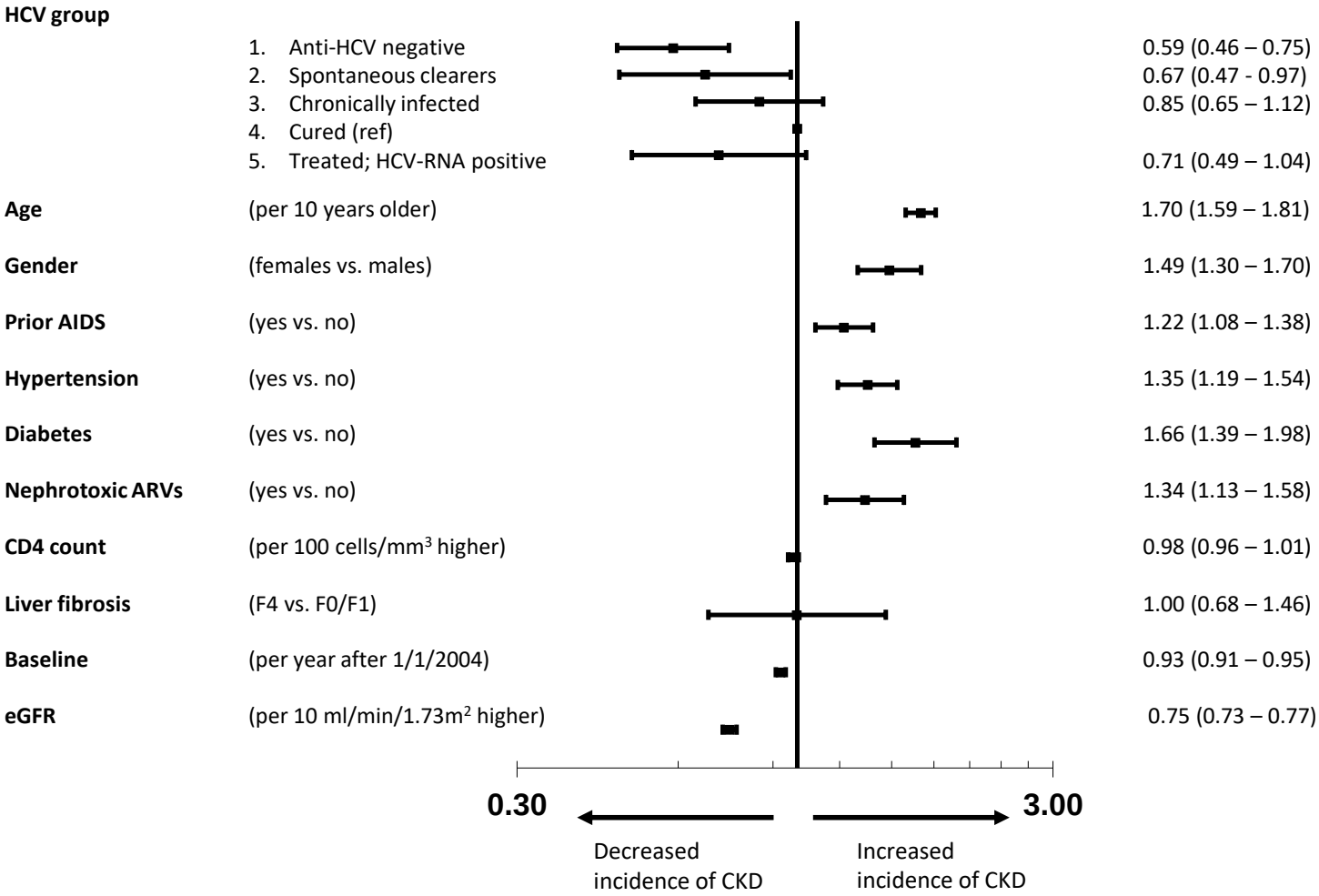
		All		Group 4; cured				Group 5; treated; HCV-RNA positive			
				No CKD		CKD		No CKD		CKD	
		N	%	N	%	N	%	N	%	N	%
All		3231	100	2553	79.0	109	3.4	531	16.4	38	1.2
Gender	M	2415	74.7	1929	75.6	76	69.7	387	72.9	23	60.5
	F	816	25.3	624	24.4	33	30.3	144	27.1	15	39.5
HIV risk	MSM	716	22.2	596	23.3	23	21.1	90	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

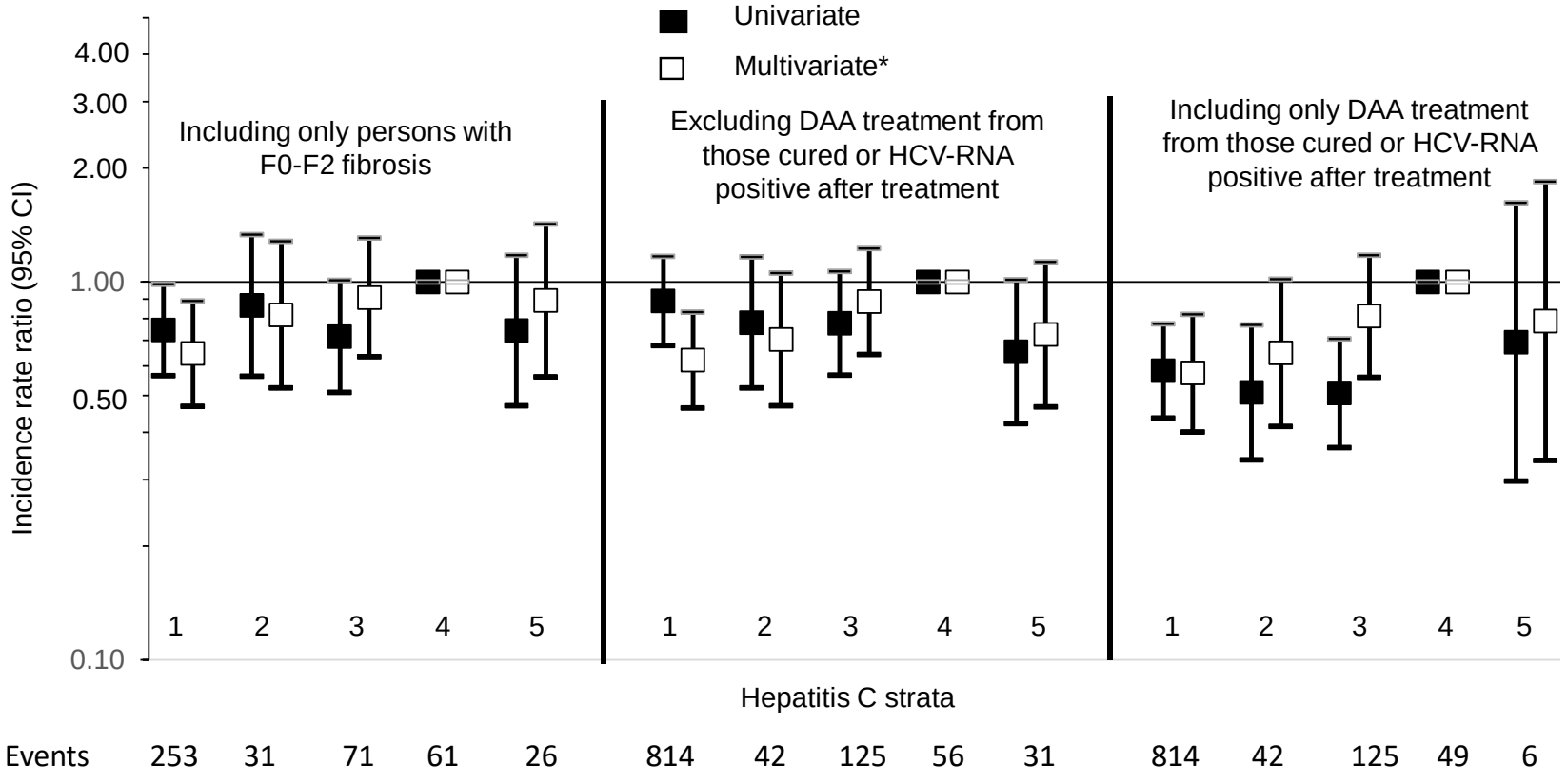
Baseline was defined as the first prospective visit in EuroSIDA after 1/1/2004 at which both eGFR and HCV serostatus were measured, and where HCV-RNA was known for those Anti-HCV positive. INF; interferon. RBV; ribavirin. DAA; direct acting antivirals. SOF; sofosbuvir. DCV; daclatasvir. SMV; simeprevir. 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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