HCV viremia increases the risk of chronic kidney disease in HIV-infected patients

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for EuroSIDA in EuroCoord

Background

- Although cART has resulted in a decrease in HIV-associated nephropathy, chronic kidney disease (CKD) is still an important cause of morbidity and mortality in HIV patients
- High prevalence of risk factors (hypertension, diabetes, smoking) for CKD in HIV patients
- In Europe around a third of all HIV patients are co-infected with hepatitis C virus (HCV)

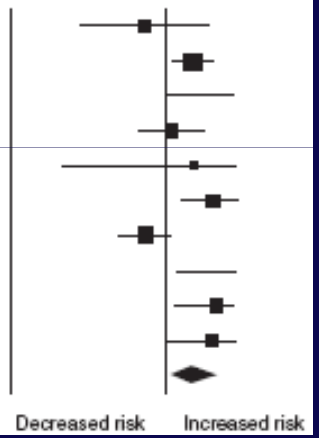
Background (2)

- HCV can cause glomerulonephritis (± cryoglobulinemia)
- HCV has been associated with higher risk of diabetes mellitus, which may contribute to the development of CKD
- HCV-related liver disease can cause CKD (hepatorenal syndrome)

The Impact of HCV coinfection of HIV-related CKD: a meta-analysis

Chronic kidney disease outcomes

Citation	Hepatitis C	No hepatitis C	RandomWtPct	Effect	Lower	Upper
Bagnis *et al.* 2006	5 / 173	30 / 756	7.35	0.73	0.29	1.85
Gardner *et al.* 2003a	135 / 537	57 / 337	16.47	1.49	1.13	1.96
Gupta *et al.* 2004	5 / 66	4 / 189	4.75	3.58	0.99	12.93
Krawczyk *et al.* 2004	18 / 83	62 / 311	13.52	1.09	0.68	1.73
Kulkarni *et al.* 2003	23 / 481	1 / 32	2.37	1.53	0.21	10.97
Lucas *et al.* 2004	55 / 1544	25 / 1416	13.49	2.02	1.26	3.22
Mocroft *et al.* 2007	32 / 922	135 / 2875	14.94	0.74	0.51	1.08
Reisler *et al.* 2003	5 / 292	6 / 1336	5.38	3.81	1.17	12.41
Szczech *et al.* 2002	25 / 804	17 / 1152	11.27	2.11	1.15	3.88
Tedaldi *et al.* 2003	16 / 267	17 / 556	10.45	1.96	1.01	3.82
Random combined (10)	**319 / 5169**	**354 / 8960**		**1.49**	**1.08**	**2.06**



Limitation: Hepatitis C diagnosis based on antibody status

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Wyatt et al; AIDS 2008

Objectives

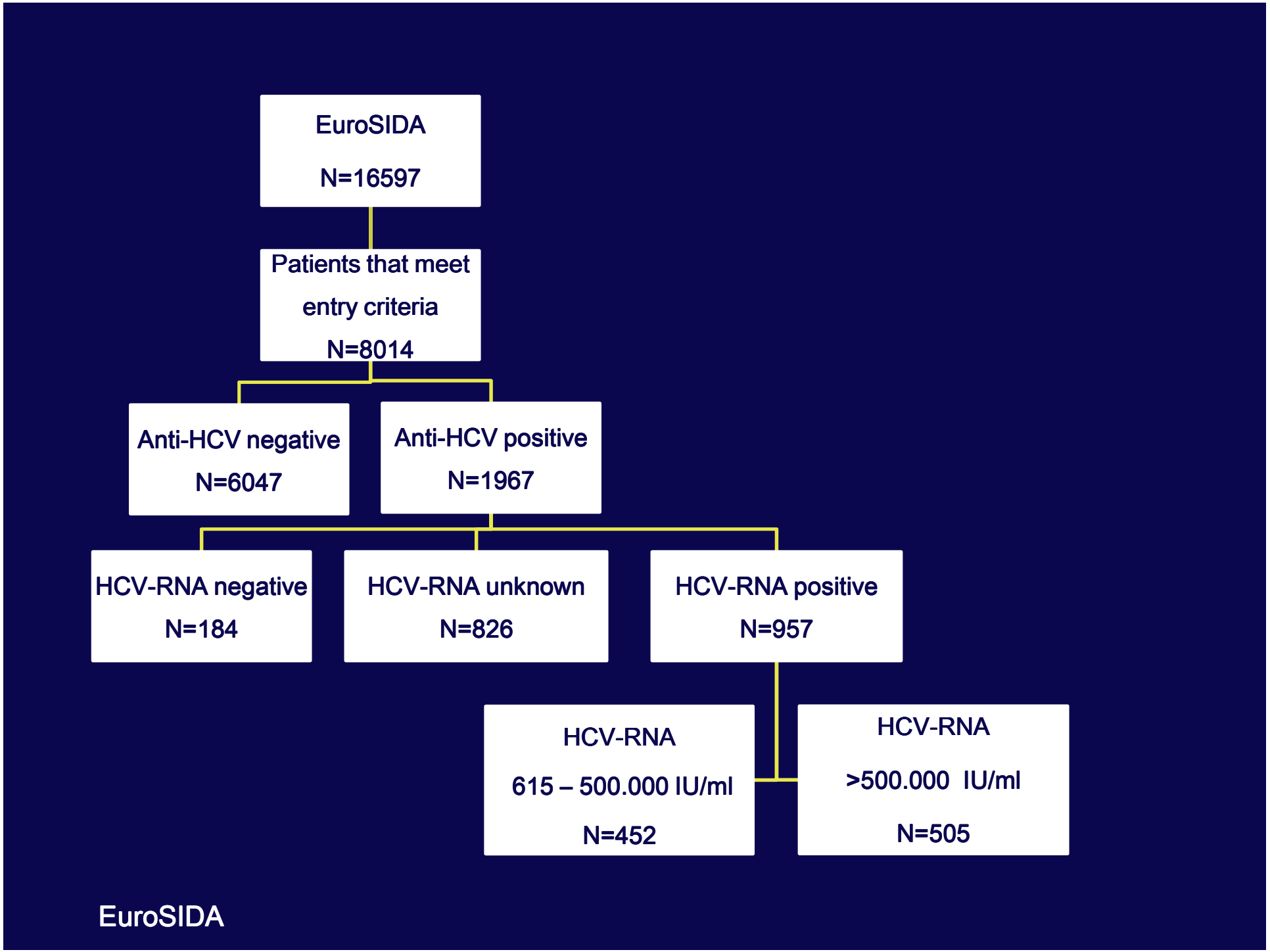
- To investigate the association of HCV viremia and genotype with incidence of CKD in the EuroSIDA observational cohort

Methods (1)

- Eligible patients:
  - ≥3 serum creatinine measurements after 01.01.04,
  - body weight measured within ≤12 months of each creatinine measurement
  - known HCVAb status
- Baseline was the first available estimated glomerular filtration rate (eGFR) (Cockcroft-Gault equation)
- $\text{eGFR} = \frac{(140-\text{age}) \times \text{weight (kg)}}{\text{Serum creatinine} \times 72} \times 0.85 \text{ (if female)}$
- eGFR standardised for body surface area

Methods (2)

- CKD:
  - i) a confirmed eGFR $\leq$ 60 mL/min/1.73m^2 for patients with eGFR >60 mL/min/1.73m^2 at baseline, or
  - ii) a confirmed 25% decline in eGFR for patients with eGFR $\leq$60 mL/min/1.73m^2 at baseline
- HCV viremic defined as HCV-RNA >615 IU/mL
  - Low viremia: 615 – 500.000 IU/ml
  - High viremia: >500.000 IU/ml
- Follow-up was from baseline to either CKD or the last eGFR measurement
- Incidence rates of CKD were compared between groups using Poisson regression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N=16597
Patients that meet entry criteria
N=8014
Anti-HCV negative
N=6047
Anti-HCV positive
N=1967
HCV-RNA negative
N=184
HCV-RNA unknown
N=826
HCV-RNA positive
N=957
HCV-RNA
615 – 500.000 IU/ml
N=452
HCV-RNA
>500.000 IU/ml
N=505
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Baseline Characteristics of 8014 HIV patients according to HCV serostatus

	Anti-HCV+ N=1967 (24.5%)	Anti-HCV– N=6047 (75.5%)
Age, median (IQR) years	39 (33 – 44)	42 (36 – 50)
Gender (male)	68.0%	75.9%
Caucasian ethnicity	91.8%	85.7%
Risk group (IDU)	71.2%	2.5%
HBsAg+	6.7%	5.9%
CD4 nadir, median (IQR) cells/μl	131 (49 – 223)	146 (51 – 245)
cART at baseline	82.8%	86.6%
Arterial hypertension	4.4%	8.8%
Smoking (current)	51.5%	28.2%
ACE inhibitor use	2.2%	4.6%
eGFR median (IQR) ml/min per 1.73m^2	100 (86.6 – 116.1)	96.6 (82.8 – 112.0)

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All P-values <0.0002

Baseline Characteristics of anti-HCV+ patients according to HCV-RNA status

	HCV-RNA+ N=957	HCV-RNA– N=184	P-value
Age, median (IQR) years	40 (36 – 45)	41 (38 – 45)	0.12
Gender (male)	68.1%	64.1%	0.29
Risk group (IDU)	74.0%	64.1%	0.0001
HBsAg+	5.4%	14.7%	<0.0001
cART at baseline	90.5%	90.2%	0.64
CD4+ nadir median (IQR) cells/µl	124 (41 – 211)	92 (23.5 – 176)	0.013
Diabetes	3.8%	5.4%	0.29
Arterial hypertension	5.0%	4.4%	0.70
Smoking (current)	56.3%	54.4%	0.21
ACE inhibitor use	2.2%	4.4%	0.94
eGFR median (IQR) ml/min per 1.73m^2	99.9 (86.8 – 115.2)	102.0 (86.7 – 114.6)	0.76

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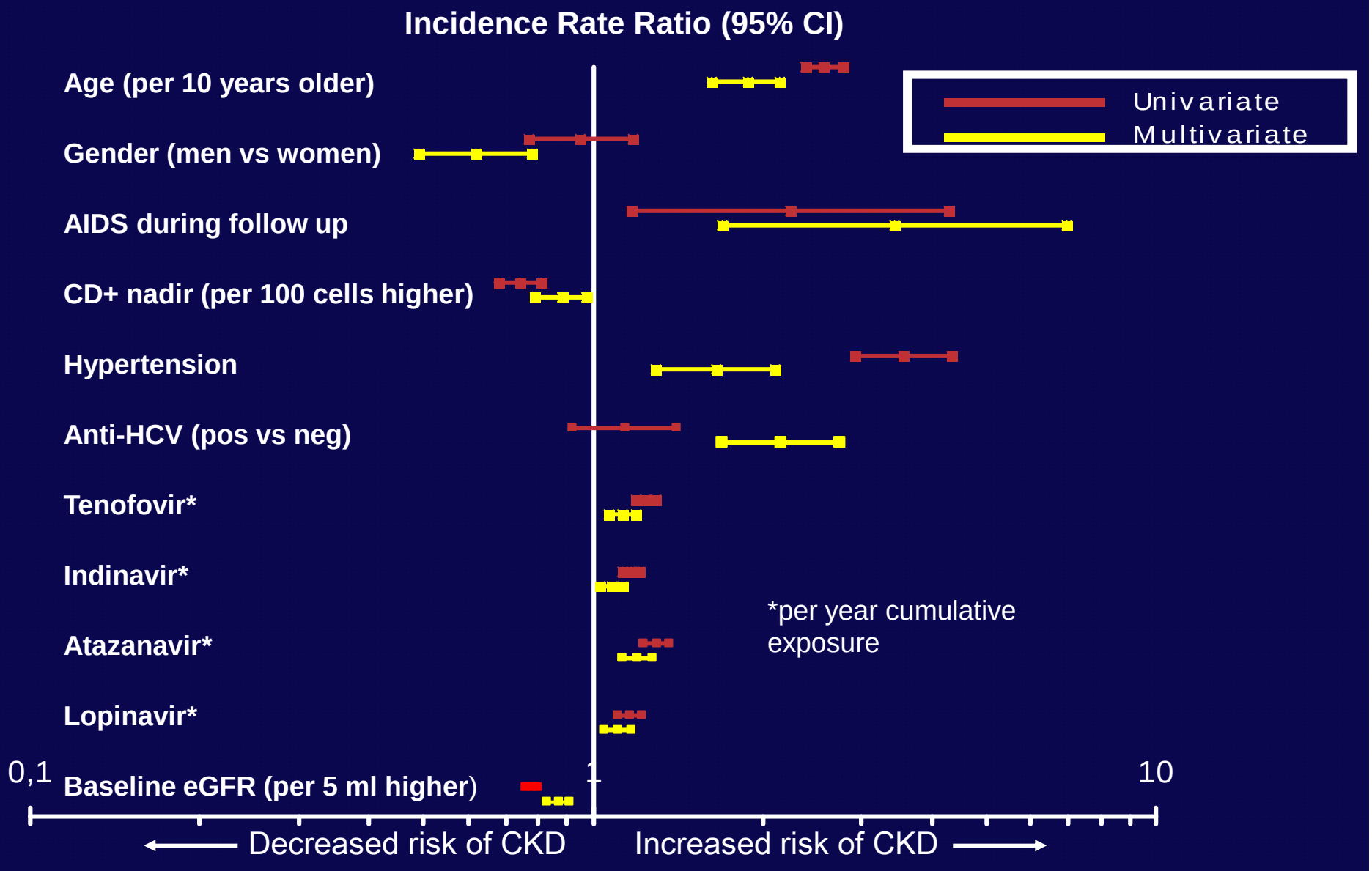
Results

- Median number of eGFR measurements/patient was 11 (IQR 7-16)
- A total of 419 patients (5.5%) progressed to CKD during 30164 PYFU
- Incidence of CKD 13.9/1000 PYFU (95% CI 12.6–15.2)

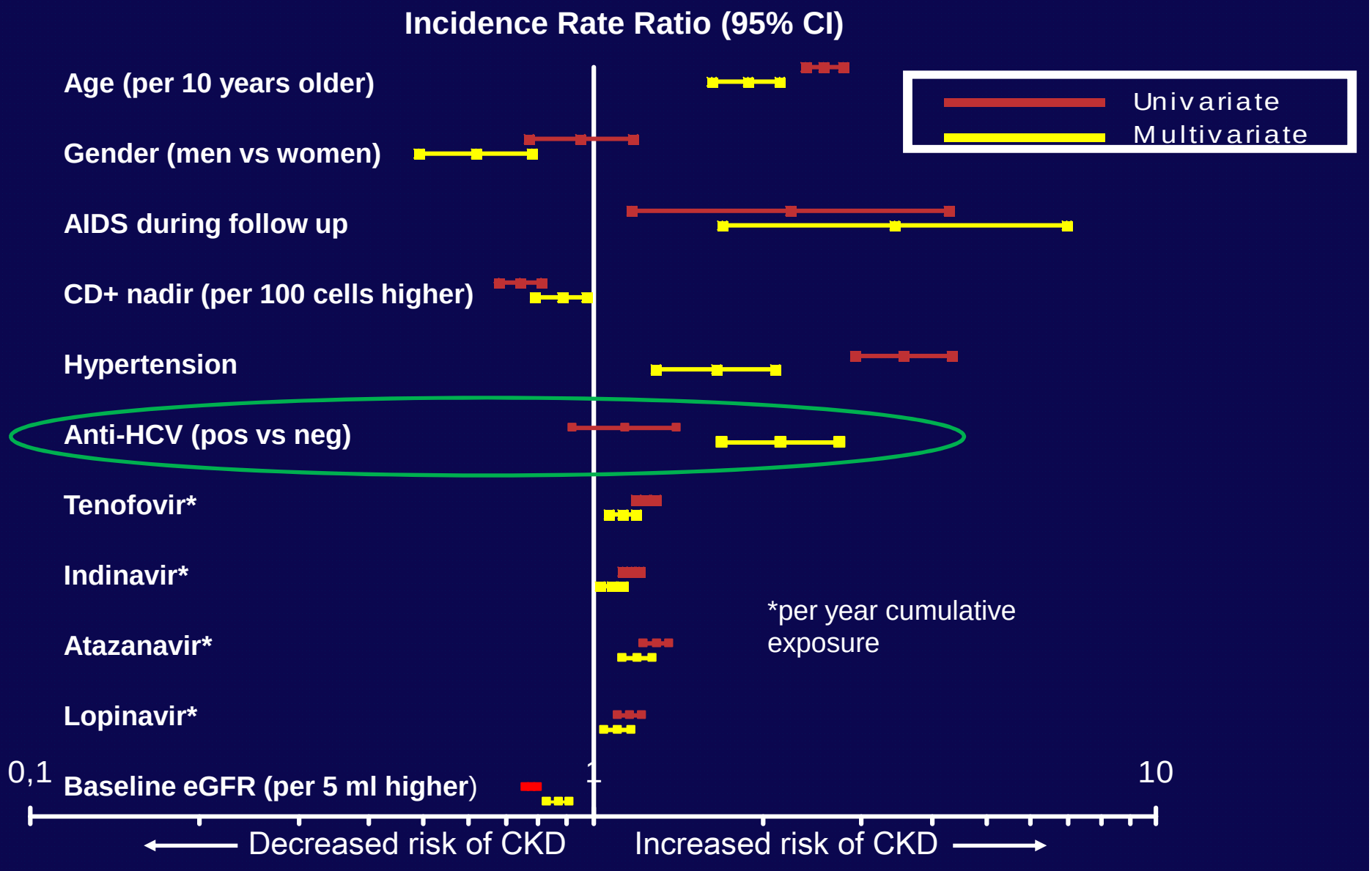
Progression to CKD

(All patients; 419 events)

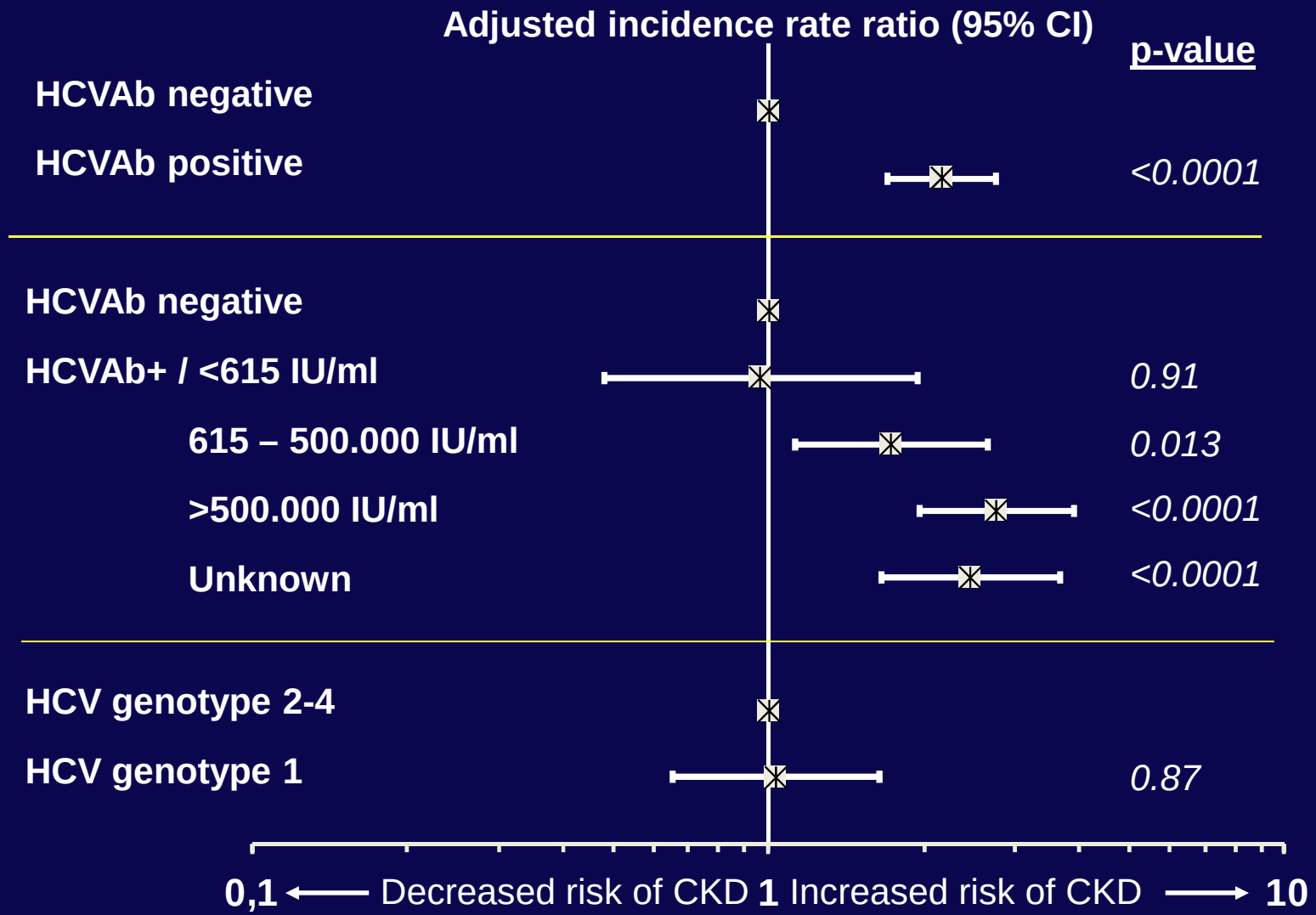


Progression to CKD

(All patients; 419 events)



Role of HCV Viremia and Genotype in Progression to CKD



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Sensitivity analysis

- Adjustment for intravenous drug use did not change the results, and was not included in the final model due to collinearity between this variable and HCV status

Summary

- Patients with chronic HCV infection were at higher risk of CKD
- Higher HCV-RNA levels were associated with an increased risk of CKD
- The risk of CKD was similar in anti-HCV negative patients and anti-HCV+ patients with resolved infection
- HCV genotype was not significantly associated with risk of CKD

Perspectives

- The mechanisms by which HCV may affect renal function are unclear and warrant further study
  - Direct effect of the virus?
  - Marker of severe liver disease?

- Should HIV/HCV coinfected patients avoid ARVs associated with risk of CKD?
- Does anti-HCV treatment reverse the decline in renal function in HCV patients with CKD?

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The multi-centre study group of EuroSIDA (national coordinators in parenthesis).

The multi-centre study group o-n EuroSIDA (national coordinators in parenthesis).
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Statement of Funding:
Primary support for EuroSIDA is provided by the European Commission BIOMED 1 (CT94-1637), BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773), the 6th Framework (LSHP-CT-2006-018632), and the 7th Framework (FP7/2007-2013, EuroCoord n° 260694) programmes. Current support also includes unrestricted grants by Gilead, Pfizer, and Merck and Co. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 108787).

Updated August 2011

EuroSIDA