a
multicentre
study

EuroSIDA

Epidemiological and virological characteristics of chronic HBV infection in HIV+ patients in Europe from 1994 to 2006

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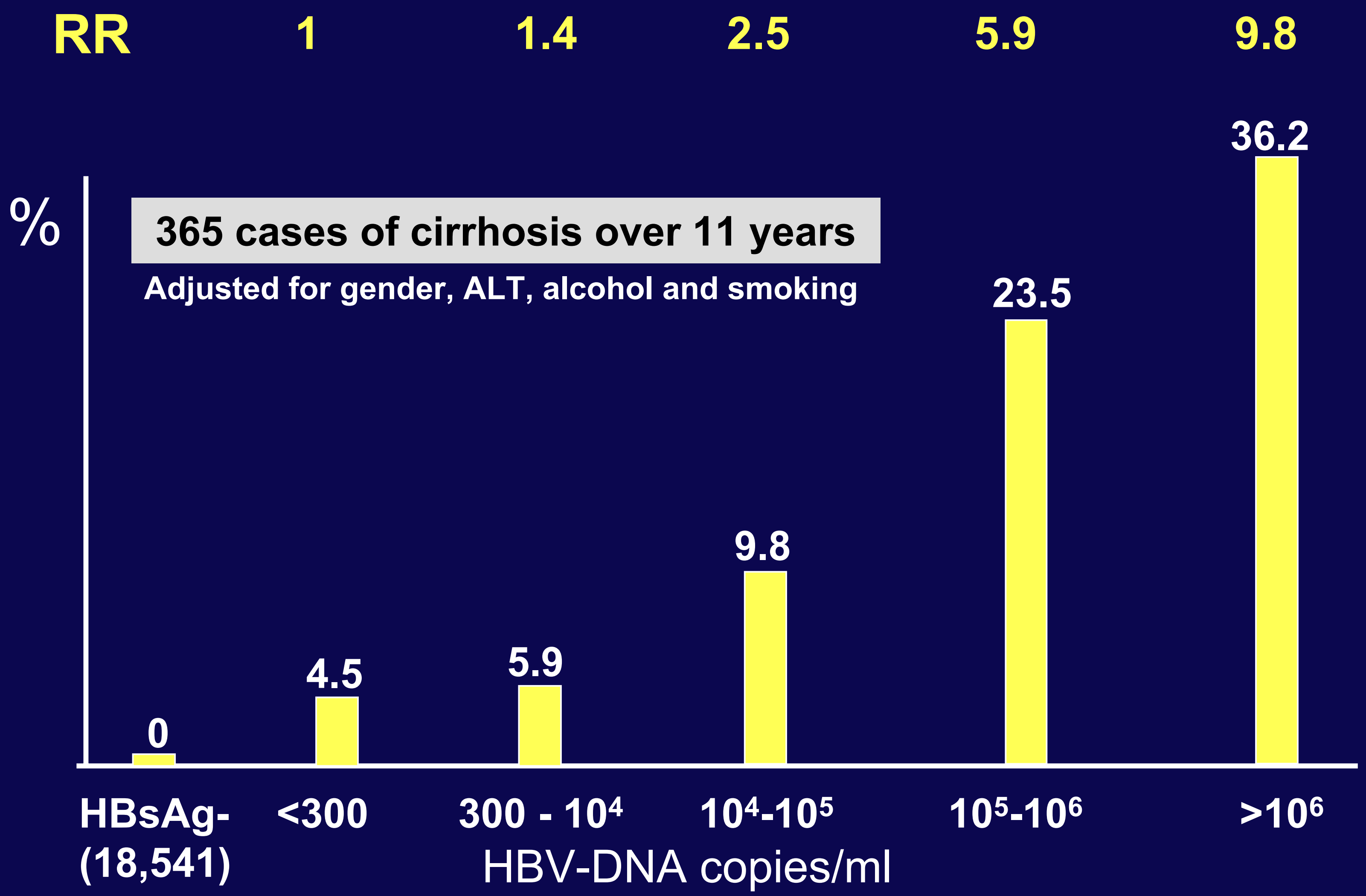
Introduction

- Both natural history and treatment outcome of hepatitis B virus (HBV) infection are influenced by genotypes and viral load.
- There is little information about factors determining HBV genotype distribution and viremia in HIV-HBV coinfected patients.

Risk of cirrhosis in HBsAg+ patients (REVEAL, n=3582)



365 cases of cirrhosis over 11 years

Adjusted for gender, ALT, alcohol and smoking

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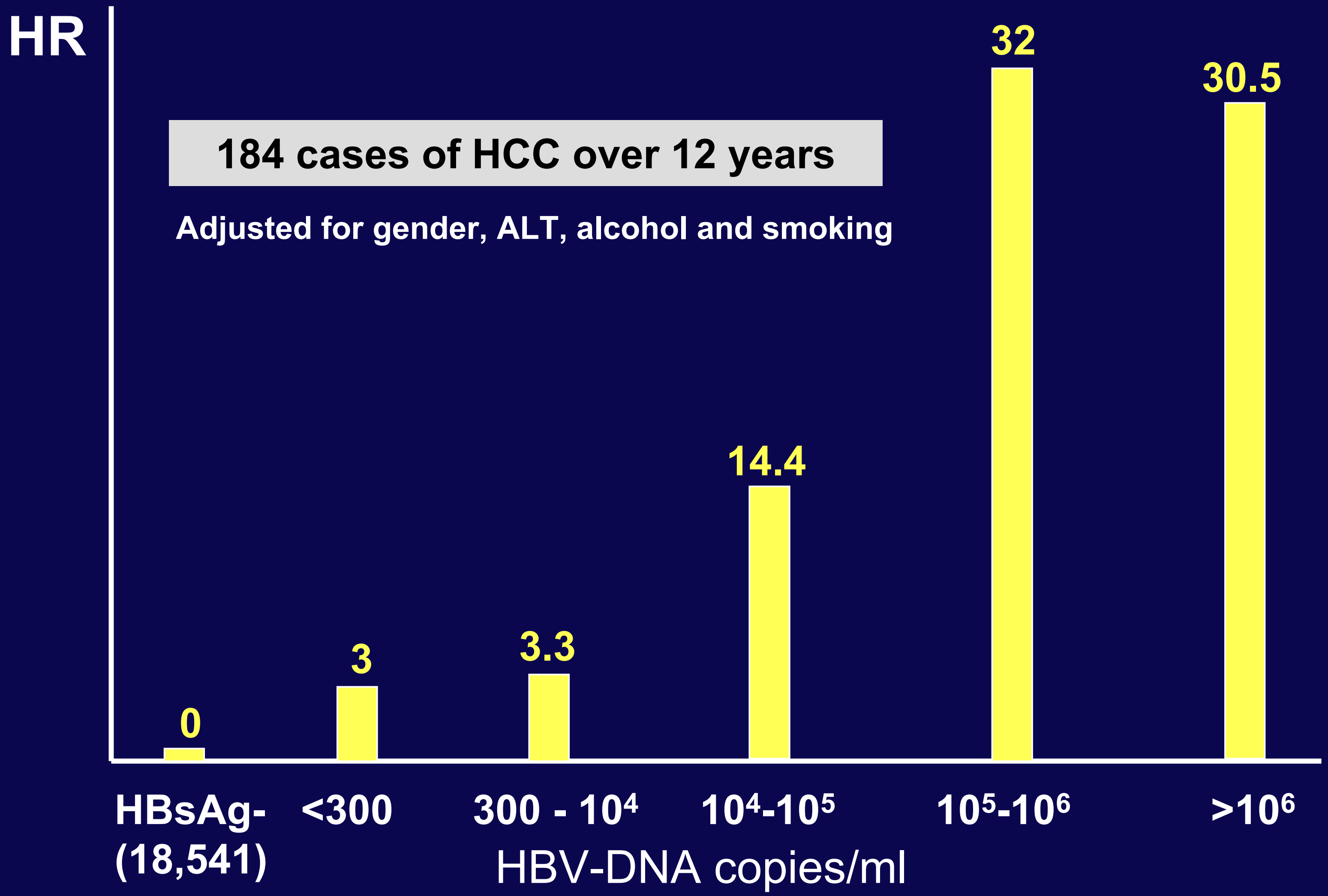
Iloeje et al. Gastroenterology 2006;130:678-86.

Risk of HCC in HBsAg+ patients (REVEAL, n=3584)



Chen et al. JAMA 2006; 245: 65-73.

HBV genotypes (9)

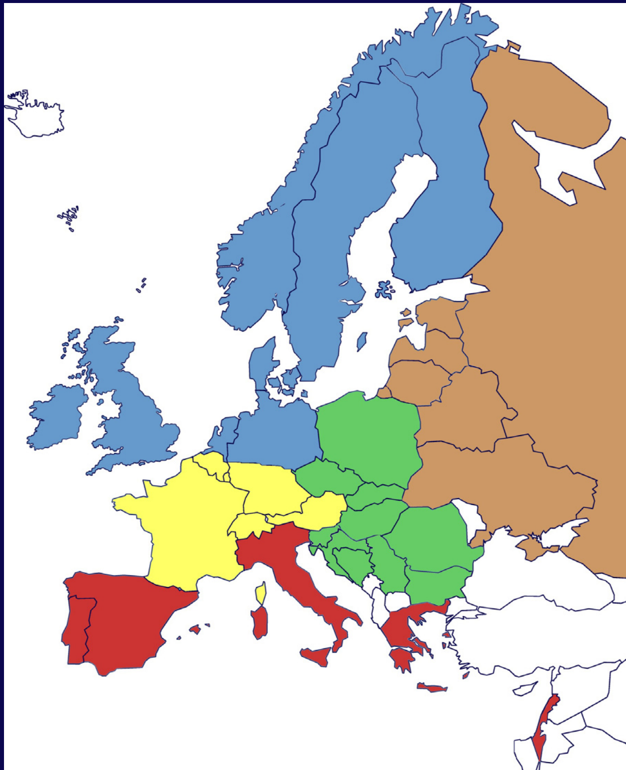
Genotype	Main characteristics
A	Predominant in North Europe and North America, often HBeAg+ and high viral load; good susceptibility to IFN;
B	Prevalent in Asia
C	Prevalent in Asia; more often HBeAg+, increased risk of HCC
D	Predominant in the Mediterranean basin; often HBeAg-neg, with or without low viral load; poor susceptibility to IFN; more frequent delta superinfection
E	Widely prevalent in Africa
F	Prevalent in Central and South America
G	In 10-20% of HIV+ patients in some series from North America and Western Europe; poor susceptibility to IFN; frequent coinfection with other genotypes; faster fibrosis progression
H	Prevalent in Central and South America
I	Recently reported in Laos & Vietnam

Aims

- To investigate the epidemiological and virological features of chronic HBV infection within EuroSIDA.

The EuroSIDA study

- Longitudinal cohort study initiated in 1994 of 16599 HIV+ patients from 103 centres in 35 countries across Europe, Israel and Argentina.
- Study collects wide range of clinical and demographic data (see www.cphiv.dk)
- Survey conducted in 2004 showed that 8.7% were HBsAg+ [1]



[1] Konopnicki et al. AIDS 2005; 19: 2117-2125.

Methods

- All HIV+ patients recruited in EuroSIDA 1994 - 2006 with positive serum HBsAg and centrally stored sera available were characterized virologically for viral load and genotype at one single reference lab.

- Serum HBV-DNA was measured using the b-DNA assay v3.0 (Siemens), which has a lower limit of detection of 357 IU/mL.

- HBV genotyping was performed using a PCR-based hybridization assay (InnoLiPA, Innogenetics) and/or the Trugene HBV 1.0 assay (Siemens).

- Median date of available serum samples was 12/98 (IQR 5/97 - 7/02).

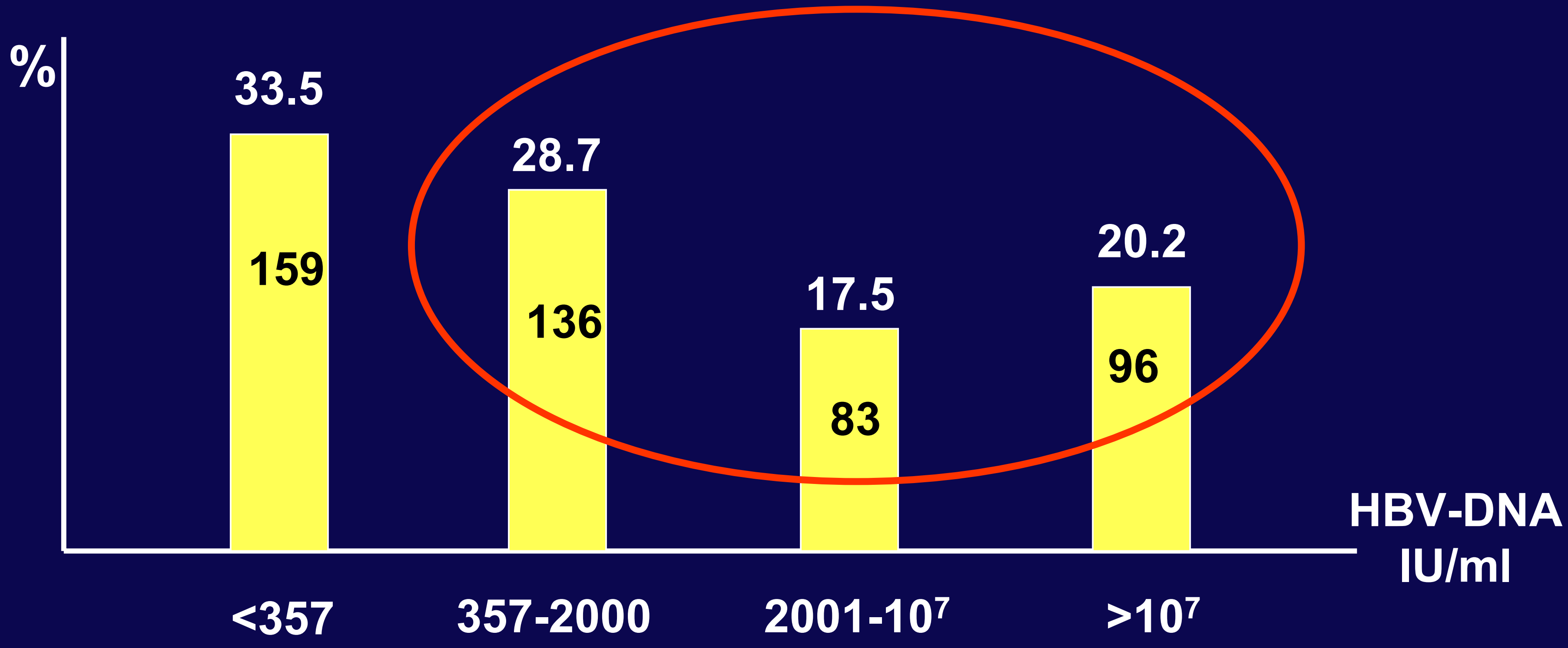
- Variables influencing HBV genotype distribution and level of viremia were assessed using logistic regression.

Results

- Of 16,505 patients in EuroSIDA, 1179 (7.1%) were HBsAg+.
- Stored samples were available for 474 (40.2%).
- Most individuals were male (84%), Caucasian (85%), and MSM (51%).
- 27% anti-HCV positive.
- 13% anti-delta positive.
- 90% on antiretroviral therapy.

HBV viremia

- Serum HBV-DNA was detectable in 315 (67.5%) out of 474 tested samples.



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Use of anti-HBV medications at the time of testing in the HIV-HBV coinfected study population

	All patients (n=474)	
	N	%
lamivudine	281	59.3
tenofovir	22	4.6
emtricitabine	4	0.8
any	293	61.8

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Stratification of serum HBV-DNA levels according to antiviral exposure at the time of testing

Serum HBV-DNA (IU/ml)	All patients	No ARV nor anti-HBV agents	ARV with 3TC (no tenofovir)*	ARV with tenofovir (+/- 3TC/FTC)	ARV with no anti-HBV drugs
	N=474	N=78	N=270	N=22	N=103
<357 (aviremic)	159	21 (26.9%)	95 (35.2%)	10 (45.4%)	33 (32.0%)
357 to 2,000	136	27 (34.6%)	77 (28.3%)	8 (36.4%)	24 (23.3%)
2,001 to 10^7	83	11 (14.1%)	56 (20.6%)	4 (18.2%)	12 (11.6%)
$>10^7$	96	19 (24.4%)	43 (15.9%)	0 (0)	34 (33.1%)

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Predictors of undetectable serum HBV-DNA

		Univariate			Multivariate		
		OR	95% CI	P	OR	95% CI	P
HCV Ab status	Negative	1.00	-	-	1.00	-	-
	Positive	1.97	1.28 – 3.04	0.0021	1.73	1.07 – 2.80	0.025
	Unknown	1.05	0.58 – 1.90	0.88	1.05	0.57 – 1.93	0.87
Baseline CD4 count	Per doubling	1.23	1.05 – 1.45	0.013	1.24	1.05 – 1.46	0.013
Delta Ab	Negative	1.00	-	-	-	-	-
	Positive	1.46	0.85 – 2.51	0.17	1.16	0.64 – 2.10	0.63
	Unknown	0.08	0.01 – 0.61	0.014	0.09	0.01 – 0.66	0.018
Years since first HBsAg+	Per year	1.07	0.99 – 1.15	0.089	1.06	0.98 – 1.14	0.14

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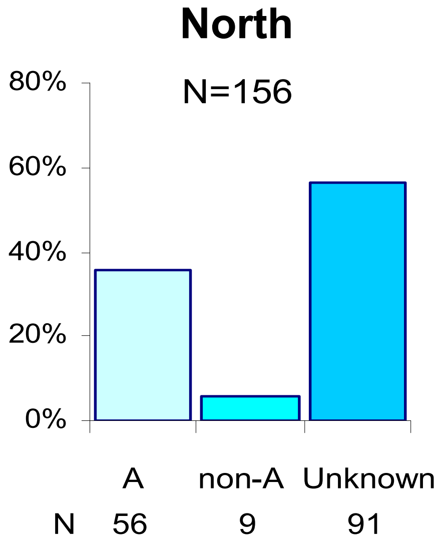
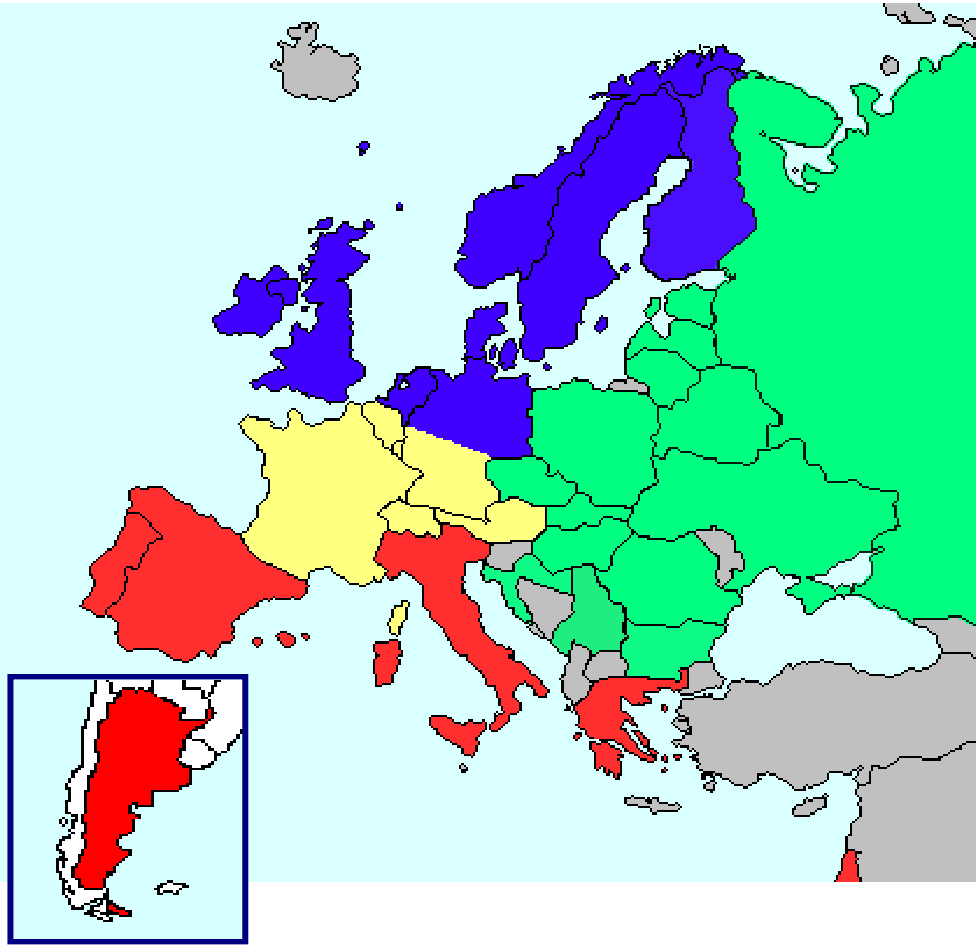
HBV genotypes

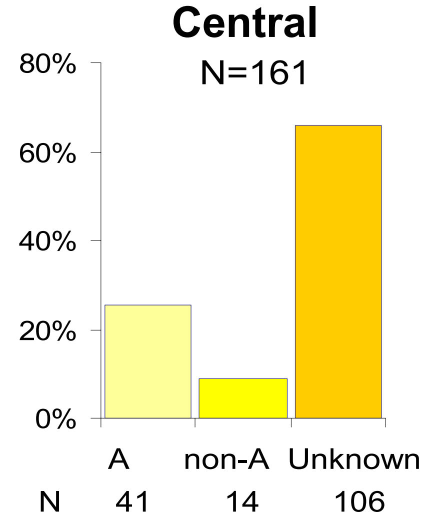
- HBV genotypes could be obtained for 167 (53%) out of 315 viremic patients.

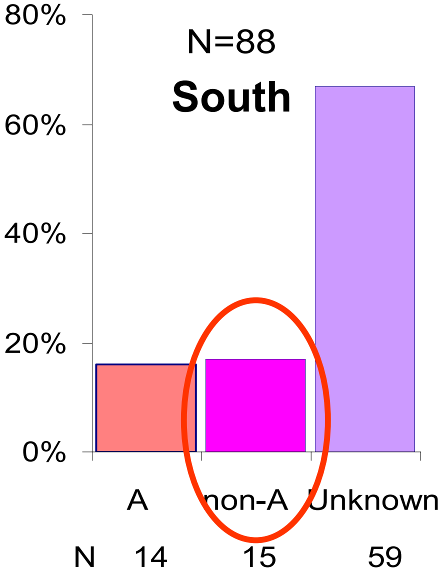
HBV genotype	%
A	72.9
D	17.1
G	1.8
E	1.2
F	1.2
C	0.6
Multiple	5.9

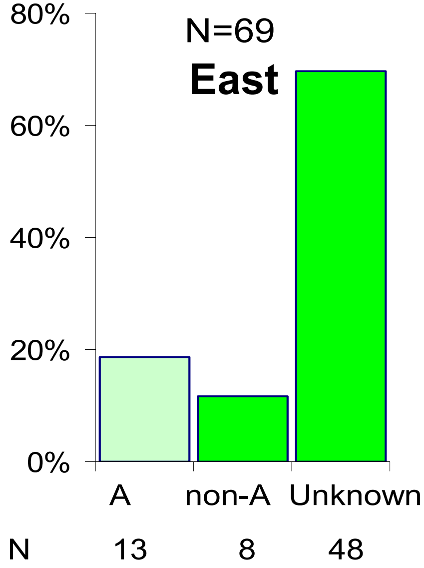
Regional Distribution of Hepatitis B virus Genotypes.



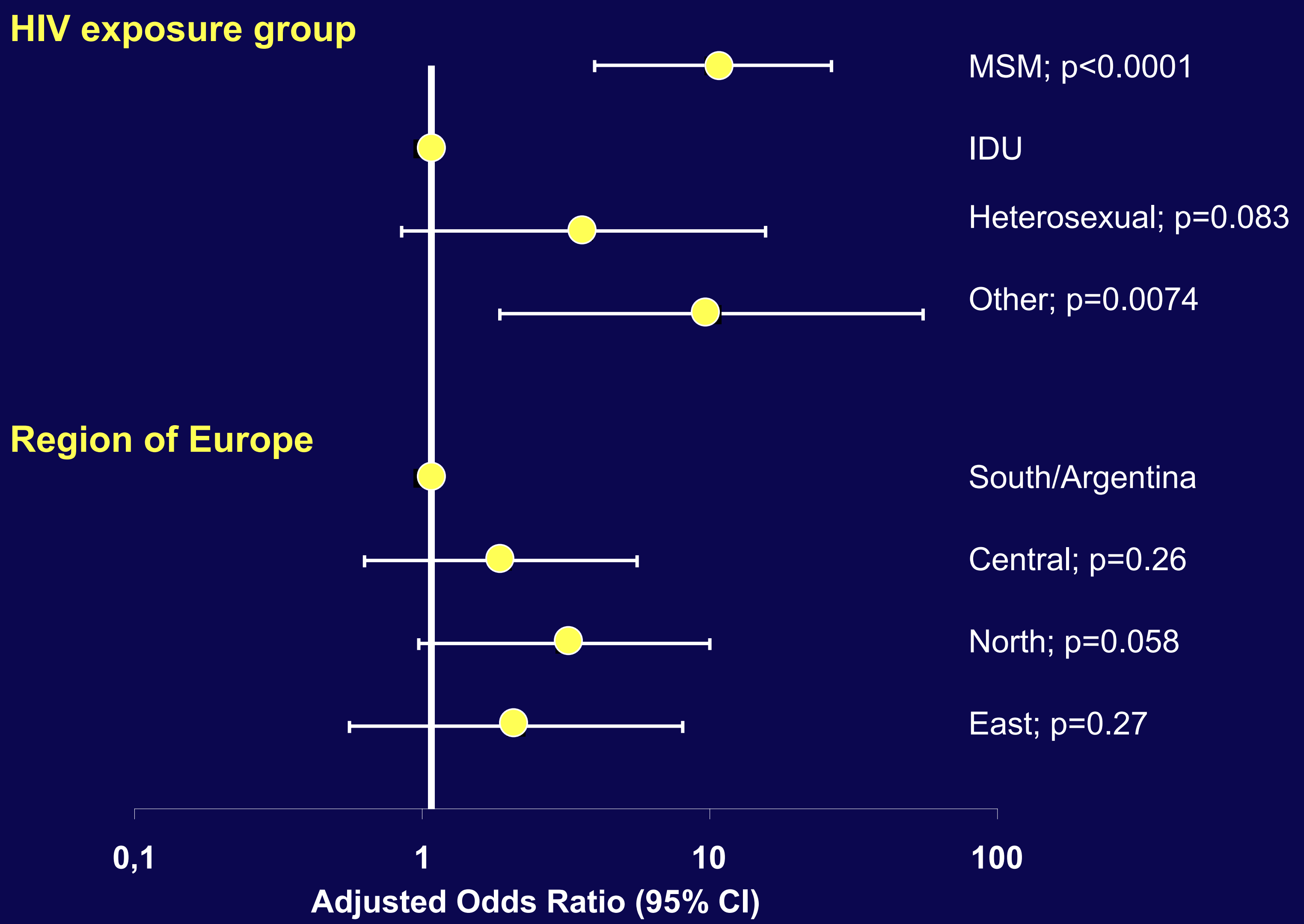








HBV genotype distribution (A vs non-A) according to risk group and region (adjusted odds)



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Summary

- More than two thirds (67.5%) of HIV/HBV coinfected patients showed detectable HBV viremia despite 62% being treated with anti-HBV active antiretrovirals*, highlighting the need for continued monitoring of HBV viral load.

- HBV viremia was above 1 million IU/mL in nearly one third (30.5%) of viremic patients, which is worrisome in terms of worse clinical outcome and difficult treatment management.

- HBV genotype A was the most common and infected nearly three quarters (73%) of patients in EuroSIDA. It was associated with MSM.

- Low CD4 counts were independently associated with a higher risk of detectable HBV viremia, indirectly supporting the current recommendation for an earlier introduction of antiretroviral therapy (CD4 >350 cells/µl), always including drugs against HBV with potency greater than 3TC alone.

**Median data testing 1998*

Caveats

- This is the largest study conducted in Europe assessing the virological characteristics of chronic HBV infection in HIV+ patients.
- Median date of tested samples was 1998, when tenofovir was still not available.
- Stored specimens for central laboratory testing were available for only 40.2% of HBsAg+ patients.
- Lower threshold for HBV viremia was 357 IU/ml, missing patients with lower but detectable values using current real-time methods (LLD 10 IU/ml).

The EuroSIDA Study Group

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

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