Hepatitis delta in HIV-infected individuals in Europe

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Background: Hepatitis delta virus (HDV) infection results in the most aggressive form of chronic viral hepatitis. There is scarce information about the prevalence, epidemiology, virological profile and natural historyof hepatitis delta in HIV patients.

Methods: From 16,597 HIV patients enrolled in EuroSIDA, 1319 (7.9%) have ever reported serum HBsAg+. At last follow-up, 1084 (6.5%) patients wereHBsAg+. The HDV substudy was carried out on 422 individuals for whom stored sera were available at the time they were HBsAg+. Anti-HDV IgG was assessed using a commercial EIA and serum HDV-RNA was quantified using a real-time PCR method.

Results: A total of 61/422 HBsAg+ carriers were anti-HDV+ (prevalence: 14.5%). Hepatitis delta predominated in intravenous drug users and for this reason in South and/or East Europe. Serum HDV-RNA was detectable in 87% of tested anti-HDV+ patients, with a median titer of $1.76x10^7$ copies/ml. Overall, delta hepatitis patients showed lower serum HBV-DNA than the rest of HBsAg+ carriers, although the inhibitory effect of HDV on HBV replication was not recognized in HBV genotype D patients.Whereas HDV was not associated with progression to AIDS, it significantly influenced the risk of death.

Conclusions: The prevalence of anti-HDV in chronic HBsAg+/HIV carriers in EuroSIDA is 14.5%. Most of these patients exhibit detectable HDV viremia. Viral interference between HBV and HDV is manifest in all but HBV genotype D carriers, in whom overt co-replication of both virusesoccurs, which might result in enhanced liver damage.Overall, delta hepatitis increases the risk of liver-related deaths and overall mortality in HIV patients.

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Introduction

Hepatitis delta virus (HDV) is a defective subviral pathogen that requires the hepatitis B virus (HBV) surface antigen (HBsAg) to be infective. Delta hepatitis is the most aggressive form of chronic viral hepatitis in humans [1]. The virus has a small (1.7 Kb) single-stranded, circular RNA genome surrounded by two antigens, a small 24-kDaHDAg and a bigger, 27-kDa HDAg. The complete viral particle includes the RNA molecule coupled by delta antigens and coated by an external lipid layer in which HBsAg is incorporated and functions as envelope protein [2].

Around 15–20 million people are infected with HDV worldwide, which overall represents 5% of individuals

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with chronic hepatitis B [3]. Endemic areas have been found in Mediterranean countries, Eastern Europe, Middle East, Central Asia, Central Africa, and the Amazonian region, while it is uncommon in Northern Europe and North America [4,5]. The virus is transmitted sexually and through parenteral exposure; outbreaks have been reported among intravenous drug users [6]. Given shared routes of transmission, HIV-infected persons are at higher risk for acquiring HDV. However, information about the prevalence, epidemiology,virological profile and natural history of hepatitis delta in HIV-infected patients is scarce.

Patients and Methods

Study population

EuroSIDA is a prospective study of 16,597 HIV-1-infected patients enrolled at 93 centres across Europe, Israel and Argentina; further details have been reported elsewhere [7]. Briefly, for each cohort the centres provide data on consecutive patients seen at the outpatient clinics beginning in May 1994 until a predefined number of patients enrol from each site. To date, eight cohorts of patients have been recruited. Data is collected prospectively at clinical sites and is extracted and sent to the coordinating centre at 6 monthly intervals. For cohorts I–III, eligible patients were those who had had a CD4 count < 500 cells/mm^3 during the previous 4 months. The CD4 count restriction was removed for cohorts IV–VII. At recruitment, in addition to demographic and clinical information, a complete hepatitis virological profile and antiretroviral treatment history is obtained, together with the most recent CD4 count and plasma HIV-RNA measurements. At each follow-up visit, details on all biochemistry, CD4 counts and plasma HIV-RNA values measured since the last follow-up visit are extracted, as are the dates of starting and stopping each antiretroviral drug received and the use of drugs for prophylaxis against opportunistic infections. The dates of diagnosis of all AIDS-defining illnesses, non-AIDS defining malignancies and other serious infections are also recorded.

The delta substudy was carried out with analyses including follow-upto March 2011and was focused on 1319 (7.9%) individuals that have ever reported serum HBsAg+. At last follow-up, 1084 (6.5%) of them wereHBsAg+. The main characteristics of the HBsAg+ population in EuroSIDA have been reported previously [8,9].

Viral hepatitis markers

Serum HBV-DNA was measured using the bDNA assay v3.0 (Siemens, Barcelona, Spain). HBV genotyping was performed using an hybridization technique (InnoLIPA, Siemens) and/or population sequencing (HBV genotyping kit, Siemens).

HDV viral markers could be examined on 422 of the HBsAg+ individuals for whom stored sera were available at the time they were HBsAg+. Anti-HDV IgG was assessed using a commercial EIA (Radim, Madrid, Spain). Serum HDV-RNA was quantified using a real-time PCR method, which has a detection limit of 10 HDV-RNA copies/mL [10].

Statistical analysis

Characteristics of patients were compared using chi-squared tests for categorical variables and non-parametric Wilcoxon or Kruskall-Wallis tests for continuous variables. Baseline was defined as the date of the serum sample. Logistic regression, using forward selection with entry criteria of $p < 0.1$, was used to identify which factors were associated with anti-HDV antibody reactivity in the study population. Multivariate Poisson regression modelling was used in time to event analyses to identify which factors were associated with progression to the clinical endpoints; death, AIDS, AIDS or death and liver related death (LRD). All data were analysed using SAS version 9.2 (Statistical Analysis Software, Cary, NC, USA).

Results

A total of 61/422 HBsAg+ carriers were anti-HDV+ (prevalence: 14.5%). The proportion of anti-HDV positive in HBsAg+ patients was higher in intravenous drug users (44/104; 42.3%) than in men who have sex with men (7/213; 3.3%) or subjects infected heterosexually (6/67; 9%) ($p < 0.001$). Likewise, the rate of anti-HDV in HBsAg+ carriers was higher in Southern (21%) and Eastern Europe (25%) than in North (9%) and Central Europe (11%) ($p=0.0032$) (Fig. 1).

Table 1 summarizes the main characteristics of the study population by HDV status. Most hepatitis delta patients in EuroSIDA were white (84%) and were receiving antiretroviral therapy at the time the study was conducted (67%), with a median CD4 count of 281 cells/μL (IQR: 184–389) and undetectable plasma HIV-RNA.

In comparison with anti-HDV-negatives, HBsAg+ patients positive for anti-HDV were younger (median age, 34 vs. 38 years; $p = 0.0007$) and more frequently female (27.9% vs. 13.9%; $p = 0.0056$), intravenous drug users (72.1% vs. 16.6%; $p < 0.0001$), positive for anti-HCV (70.5% vs. 21.1%; $p < 0.0001$), lived in South and/or East Europe (52.4% vs. 26.6%; $p < 0.0032$), and were infected by HBV genotype D (50% vs. 12%; $p < 0.01$). In a multivariate analysis, however, the only independent predictor of anti-HDV+ in HBsAg+ carriers was

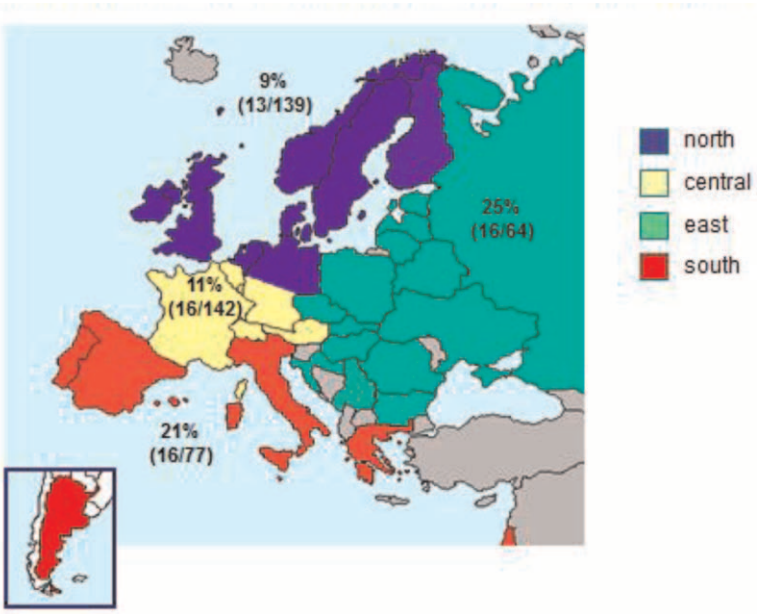

Fig. 1. Prevalence of Anti-HDV Ab in serum HBsAg+ Patients in EuroSIDA.

intravenous drug use (odds ratio: 5.99; 95% confidence interval: 2.28–15.71; p = 0.0003).

HBV genotype distribution in anti-HDV-positive patients was as follows: D (50%), A (27%), AD (14%), AG (4.6%), and ADG (4.6%). By contrast, HBV genotypes in anti-HDV-negative patients were as follows: A (78%), D (12%), G (2.4%), F (1.6%), AD (1.6%), AG (1.6%), E (1.6%), F (1.6%) and C (1%).

For 38 individuals positive for anti-HDV, both serum HBV-DNA and HDV-RNA could be measured quantitatively. Both viruses were viremic in 58%, only HDV viremic in 29%, none had HBV exclusively viremic and 13% were aviremic for both viruses.Overall, 31/38 (86.8%)of anti-HDV+ patients had detectable serum HDV-RNA, with a median titer of 1.76 x 10^7 copies/mL (IQR: 2.59 x 10^3 – 8.89 x 10^9).

Table 1. Main characteristics of HIV-infected patients with chronic hepatitis B according to hepatitis delta status.

Variable	AllHBsAg + patients	HDV Ab-positive	HDV Ab-negative	p
No. (%)	422	61 (14.5)	361 (85.5)	
Median age (years)	37	34	33	0.0007
Malegender (%)	84.1	72.1	86.1	0.0056
Whiteethnicity (%)	357 (84.6)	303 (83.9)	54 (88.5)	0.36
Risk group (%)				<0.0001
MSM	213 (50.5)	7 (11.5)	206 (57.1)	
IDU	104 (24.6)	44 (72.1)	60 (16.6)	
Heterosexual	67 (15.9)	6 (9.8)	61 (16.9)	
Others	38 (9.0)	4 (6.5)	34 (9.4)	
HIV parameters				
Median CD4 count (cells/μL)	285	281	294	0.53
Median nadir CD4 count (cells/μL)	142	143	141	0.90
Median plasma HIV-RNA (log cop/mL)	2.7	2.7	2.7	0.77
Patients on HAART (%)	310 (73.5)	41 (67.2)	269 (74.5)	0.23
Patients on lamivudine, tenofovir or emtricitabine (%)	299 (70.9)	41 (67.2)	258 (71.5)	0.50
Viral hepatitis markers				
HCV-Ab positive (%)	119 (28.2)	43 (70.5)	76 (21.1)	<0.0001
Serum HBV-DNA positive (%)	61	59	63	0.54
Median HBV-DNA (IU/mL)	19,346	949	24,522	0.003
SerumHBV-DNA >10^7 IU/ml (%)	17	11	20	0.11
HBV genotypes (%)				<0.0001
D	39	50	12	<0.01
A	56	27	78	<0.01

∗It also includes Argentina (13 HBsAg + patients, all of them anti-HDV negative).

In anti-HDV+ patients, an association was found between HBV genotype distribution and serum HBV-DNA levels. In patients with serum HBV-DNA $>10^7$ IU/ml, the only HBV genotype found was D, while in anti-HDV negative patients,high levels of HBV-DNA were seen in up to 81% of HBV genotype A cases.

The proportion of subjects with detectable HBV viremia was similar in patients with or without anti-HDV (59% *vs* 63%, respectively, p = 0.54). However, the median serum HBV-DNA titer was significantly lower in anti-HDV-positive than in anti-HDV-negative patients (949 vs 24,522 IU/ml, respectively; p = 0.003). Moreover, the proportion of patients with serum HBV-DNA above the upper limit of detection ($>10^7$ IU/ml) tended to be higher in anti-HDV-negative than in anti-HDV-positive patients (20% vs 11%, p = 0.11).

Table 2 records the multivariate regression analysis in which factors associated with serum HBV-DNA levels were examined. Given that some antiretroviral agents (i.e., lamivudine, tenofovir or emtricitabine) also exert anti-HBV activity, their use was included in the model. Anti-HDV seropositivity together with positive and unknown HDV-RNA were associated with lower HBV-DNA. Likewise, HBV genotypes other than D and Northern Europe were also associated with lower HBV-DNA levels.

A longitudinal analyses of HBsAg+ patients in EuroSIDA allowed assessment of the proportion of patients that progressed to AIDS (31 events), to death (76 events), to AIDS and/or death (91 events), and to liver related death (21 events). As shown in Table 3, anti-HDV positivity was significantly associated with death from any cause, progression to AIDS or death and progression to liver related death, but not to progression to AIDS alone.

Discussion

The overall prevalence of anti-HDV in HIV-infected patients with chronic hepatitis B in EuroSIDA is 14.5%. Chronic hepatitis delta predominates in intravenous drug users, being present in up to 42% of those positive for HBsAg. The larger representation of intravenous drug users in South and East Europe in comparison with other regions explains that anti-HDV was particularly common in those geographical areas. Likewise, it explains the association between anti-HDV and anti-HCV positivity, as HCV is poorly transmitted sexually whereas it is very efficiently acquired through parental routes [11].

More than 85% of anti-HDV patients in EuroSIDA exhibited detectable HDV viremia in a single cross-sectional determination. It is worth mentioning that longitudinal testing most likely would have revealed circulating serum HDV-RNA in most of the remaining anti-HDV patients, as fluctuating levels of HDV-RNA and HBV-DNA are common in these subjects [12]. Viral interference between HBV and HDV is well known [12,13]. Interestingly, in our study it was particularly recognized in HBV genotype A patients superinfected

Table 2. Predictors of serum HBV-DNA levels.Multivariate regression model.

Variable		Estimate	95% confidenceinterval		p
Gender	Female	−0.0923	−0.3678	0.1831	0.5112
	Male	0	0	0	
Race	Non-white	−0.1693	−0.444	0.1053	0.2269
	white	0	0	0	
Age (per 10 years)	0.0616	−0.0422	0.1654	0.245	
Baseline CD4 count (per 100 cells/mm^3)	0.0042	−0.0584	0.0668	0.8947	
CD4 nadir (per 100 cells/mm^3)	−0.0418	−0.1366	0.0529	0.3864	
Baseline plasma HIV-RNA ($\log_{10}$ copies/ml)	0.059	−0.0219	0.1399	0.1528	
Use of anti-HBV drugs	Lamivudine	−0.1776	−0.4052	0.0499	0.126
	Tenofovir	−0.0021	−0.4164	0.4121	0.9919
	Emtricitabine	−0.7497	−1.7887	0.2893	0.1573
Anti-HDV & HDV-RNA	Positive & unknown	−0.8021	−1.2297	−0.3745	0.0002
	Positive & negative	−0.3092	−1.1975	0.579	0.495
	Positive & positive	−0.6087	−0.9801	−0.2373	0.0013
	Negative	0	0	0	
HCV Ab	Unknown	0.0953	−0.1996	0.3903	0.5263
	Positive	0.0296	−0.2272	0.2863	0.8214
	negative	0	0	0	
HBV genotype	Unknown	−3.8011	−4.2264	−3.3758	<.0001
	A	−0.4996	−0.9672	−0.0319	0.0363
	Others	−1.1374	−1.7584	−0.5164	0.0003
	D	0	0	0	–
Geographical region	South + Argentina	0.2219	−0.1102	0.554	0.1903
	West	0.2397	−0.0802	0.5596	0.1419
	North	0.3693	0.0458	0.6928	0.0253
	East	0	0	0	

In bold, variables with statistical significance.

Table 3. Predictors of progression to AIDS, death or either in the HBsAg +, HIV study population.

Variable	Progressiontodeath			Progressionto AIDS			Progression to AIDS or death			Progressionto LRD		
	IRR	95% CI	p	IRR	95% CI	p	IRR	95% CI	p	IRR	95% CI	P
Anti-HDVpos vs.neg	2.2346	1.1664 4.2814	0.0154	1.6041	0.5641 4.5617	0.3755	2.1702	1.2176 3.8678	0.0086	4.4403	1.4554 13.5472	0.0088
CD4 (per 100 cells/mm^3)*	0.7047	0.583 0.8518	0.0003	0.4781	0.3272 0.6985	0.0001	0.6917	0.5819 0.8223	<.0001	0.3515	0.2053 0.602	0.0001
CD4 nadir (per 100 cells/mm^3)	0.7547	0.5535 1.029	0.0752	1.2799	0.8142 2.0118	0.2849	0.8426	0.6434 1.1035	0.2135	0.5441	0.2623 1.1285	0.102
Plasma HIV-RNA (log_{10} copies/ml)*	1.3096	1.0871 1.5776	0.0045	1.3952	1.0395 1.8725	0.0265	1.318	1.1113 1.5632	0.0015	0.9832	0.6985 1.384	0.9227
Antiretroviral therapy	0.6305	0.3491 1.1387	0.1262	0.9969	0.3948 2.5177	0.9948	0.8018	0.463 1.3886	0.4305	0.577	0.1826 1.8236	0.349
Male vs. female	0.5019	0.2522 0.9986	0.0495	1.0929	0.3662 3.2613	0.8735	0.5322	0.2887 0.9811	0.0433	0.58	0.16 2.1021	0.407
Age (per 10 years)	1.9458	1.5042 2.5171	<.0001	1.1973	0.7726 1.8554	0.4205	1.6678	1.3146 2.1158	<.0001	2.0735	1.2338 3.4846	0.0059
White vs. others	1.4047	0.6566 3.005	0.3811	0.9129	0.3353 2.4852	0.8584	1.1831	0.6155 2.2741	0.6139	2.4494	0.4823 12.4386	0.2799
HCV Ab pos vs.neg	1.2738	0.74 2.1926	0.3825	1.2242	0.5173 2.8972	0.6453	1.1223	0.6785 1.8564	0.6532	0.8557	0.2852 2.5676	0.7811
HBV genotypes: A vs. D	1.6783	0.4642 6.0673	0.4297	2.3124	0.2121 25.2079	0.4916	1.5694	0.5062 4.8655	0.4349	0.5787	0.0835 4.009	0.5797
Others vs. D	1.3567	0.2845 6.4698	0.7019	1.1896	0.0639 22.1587	0.9074	1.0521	0.2504 4.4197	0.9447	0.4626	0.0306 6.9884	0.5779
Unknown vs. D	1.1091	0.3255 3.7791	0.8685	2.6682	0.2837 25.0951	0.3908	1.1177	0.3835 3.2576	0.8385	0.5982	0.1025 3.4905	0.568
Geographial region: South vs. North	0.9011	0.4672 1.7379	0.756	1.3922	0.5083 3.8136	0.5198	1.0661	0.5881 1.9327	0.833	1.5443	0.4317 5.5243	0.504
Westvs. North	0.5784	0.3172 1.055	0.0742	0.8994	0.3585 2.2566	0.8213	0.6205	0.3593 1.0715	0.0869	1.3737	0.474 3.9814	0.5587
East vs. North	0.5843	0.236 1.4471	0.2456	Non-estimable	0.4808 0.1964	1.1771	0.1089	Non-estimable				

IRR, incidence rate ratio; 95% CI, 95% confidence interval; HDV, hepatitis delta virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

with HDV, whereas overt co-replication of HBV and HDV was more common in HBV genotype D carriers. Hypothetically, this last group of patients replicating both HBV and HDV might experience enhanced liver damage [14]. This differential effect of HDV superinfection on the replication of distinct HBV variants has been noticed for some lamivudine-resistant HBV mutants, which impair HDV replication compromising viral secretion [15]. Our findings suggest that viral interference between HDV and HBV mightbe more frequent over HBV genotype A than D. A more limited production of HBsAg by HBV genotype A than D might contribute to explain this observation. In our study we did not record information on HBeAg, which is associated with greater serum HBsAg levels [16,17] and is more frequently positive in adults infected by HBV genotype A than D [12].

Treatment of chronic hepatitis delta is a huge challenge [18]. HDV replicates using a human hepatocyte polymerase; so, nucleos(t)ide analogues designed to act as inhibitory competitors of viral polymerases do not block HDV replication directly. Current recommended therapy for chronic hepatitis delta consist in the administration of pegylated interferon-α for at least 12 months [19,20]. Future therapeutic options may include prenylate inhibitors [21]. In the meantime, several reports have highlighted that potent nucleos(t)ide analogues as tenofovir may be beneficial in a subset of patients with delta hepatitis, as they may experience normalization of liver enzymes, reduction or negativization of HDV-RNA and even clearance and/or seroconversion of serum HBsAg [22,23]. Similar results have not been obtained using other nucleos(t)ide analogues, such as lamivudine [24] or adefovir [20]. The potential benefit of tenofovirin delta hepatitis, however, has been mainly limited to HBV genotype A and/or HBeAg+ carriers. Although the underlying reason for it remains unclear, a reduced production and availability of the HBsAg protein in HBV genotype A patients compared to other HBV genotypes, such as D, might explain why potent suppressors of HBV replication might impair HDV production in some HBV variants preferentially than in others.HBsAg production and HBV replication breaks down in patients with HBeAg-negative chronic hepatitis B, when a growing proportion of HBsAg becomes to be produced from HBV genomes integrated in the host chromosomes instead of from non-integrated cccDNA in hepatocytes [16]. Although we did not record HBeAg in our patient population, it is reasonable to assume that HBeAg-negative would have been more frequent in HBV genotype D than A, in line with observations from others [12].

Our study has several limitations. We already mentioned above that HBeAg was not recorded in our study population, and that it may have influenced indirectly the association found between HBV genotypes and serum

HDV-RNA levels. Another limitation of our study was that HDV markers were examined in only a fraction of HBsAg+ carriers. Overall 422 out of 1319 (32%) individuals that had ever reported serum HBsAg+ in EuroSIDA were tested for anti-HDV antibodies, given that no stored sera were available for the rest at the time they were HBsAg+. Even so, the number of patients positive for anti-HDV antibodies in our study (61) is one of the largest that has been characterized virologically so far. Moreover, we are confident about the representativeness of our patient population, because in a study conducted in Spain over 37 delta hepatitis patients negative for HIV [12], the proportion of viremic patients for either HBV and/or HDV was comparable to ours, although there was a trend for a greater rate of dually viremic individuals in our HIV population than in that HIV-negative series (58% vs 40%, respectively). Hypothetically, immunodeficiency might ameliorate viral interference phenomena that characterize multiple viral hepatitis co-infections, allowing concomitant replication of multiple viruses [25,26].

Most guidelines recommend that all HBsAg+ patients should be tested for anti-HDV antibodies [27–29]. Given that a fraction of HDV-seropositive individuals may not actively replicate the virus, serum HDV-RNA should be measured and treatment be considered in patients with detectableviremia, given that chronic hepatitis delta is associated with a high risk of cirrhosis in HIV-infected patients [30].Moreover, in our studywe reported for the first time that hepatitis delta was further predictive of increased risk of liver-related death and overall mortality in HIV patients.Failure to exclude HDV infection in HBsAg carriers may result in an unexpected worse outcome and trigger unnecessary search for other etiologies of liver disease.

Role of each author: VS, JR, JL and LP designed the study; EP and VS were responsible for the virological analyses; DG did the statistical analyses; VS, JR, LP, JL, AdM, AH, CL, FA and SdW helped to collect laboratory and clinical information and reviewed the manuscript.

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Conflicts of interest

None declared.

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