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The role of HIV/HBV/HCV triple infection in end stage liver disease (ESLD) and all cause mortality in Europe

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BACKGROUND and AIMS

- Hepatitis B (HBV) and Hepatitis C(HCV) coinfections are an important cause of morbidity and mortality in PLWH (1).
- Previous studies have shown increased rates of ESLD, hepatic decompensation, cirrhosis and hepatocellular carcinoma in those with HIV/HBV or HIV/HCV compared with HIV alone (2,3).
- Studies of ESLD or mortality, in those with HIV/HBV/HCV (triple infection) compared to dual infection with HBV/HIV or HIV/HCV are lacking

METHODS

- EuroSIDA participants aged >18 with known HBsAg, anti-HCV and HCVRNA status were included; baseline was defined as first date > 1/1/2001 after EuroSIDA enrolment when HBV, anti-HC and HCV RNA was known.
- Six groups were defined;
  1. *HBsAg negative, HCV antibody negative (HIV)*
  2. *HBsAg positive, HCV antibody negative (HIV/HBV)*
  3. *HBsAg negative, HCV antibody positive, HCV-RNA positive (HIV/HCVA/HCVRNA+)*
  4. *HBsAg positive, HCV antibody positive, HCV-RNA positive (HIV/HBV/HCVA/HCVRNA+; triple infected)*
  5. *HBsAg negative, HCV antibody positive, HCV-RNA negative (HIV/HCVA/HCVRNA-)*
  6. *HBsAg positive, HCV antibody positive, HCV-RNA negative (HIV/HBV/HCVA/HCVRNA-)*

Table 1 Study characteristics at baseline

		All	
		N	%
All		16584	100.0
Strata: HIV		9611	58.0
HIV/HBV		720	4.3
HIV/HCVA/HCVRNA+		4108	24.8
HIV/HBV/HCVA/HCVRNA+		298	1.8
HIV/HCVA/HCVRNA-		1682	10.1
HIV/HBV/HCVA/HCVRNA-		165	1.0
Gender	Male	12279	74.0
HIV risk	MSM	6422	38.7
	IDU	4263	25.7
HIV-RNA	<500 copies/ml	11476	69.2
Previous	ESLD	197	1.2
Smoking status	Never	4569	27.6
	Current	8629	52.0
Liver Fibrosis	Stage 0/1	6896	41.6
		Median	IQR
Age		41	35-49
Baseline	Mm/yy	1/06	1/01-5/12
CD4	/mm^3	445	290-637

PLWH with triple infection had higher rates of ESLD and all-cause mortality than those with HIV/HCVA/HCVRNA+. After adjustment, the increased rate of ESLD in triple infection vs. HIV/HCVA/HCVRNA+ was not statistically significant, possibly due to limited power, but the higher rates for all-cause mortality remained

- Poisson regression was used to assess association between current HBV/HCV/HCVRNA status, ESLD and all cause mortality.

RESULTS

- Overall, 16,584 persons were included (Table 1).
- 458 ESLD events occurred during 153,899 PYFU (IR 3.0/1000 PYFU; 95% CI 2.7–3.3). The distribution of events is shown in Figure 1.
- 2035 deaths occurred during 154,913 PYFU (IR 13.1/1000 PYFU; 95% CI 12.6–13.7). The causes of death, including data to the end of 2018, are shown in Figure 2.
- Crude incidence rates of ESLD and all-cause mortality were higher in HIV/HBV/HCVA/HCVRNA+ than in all other groups (Table 2).
- After adjustment (Table 2), compared to those with HIV/HBV/HCVA/HCVRNA+, PLWH with HIV/HCVA/HCVRNA+ had statistically significantly lower rates of all-cause mortality (aIRR 0.75; 95% CI 0.56–1.00) whereas the lower rates of ESLD was of a similar magnitude but did not reach statistical significance, possibly due to the smaller number of ESLD events (aIRR 0.71; 95% CI 0.47–1.06).

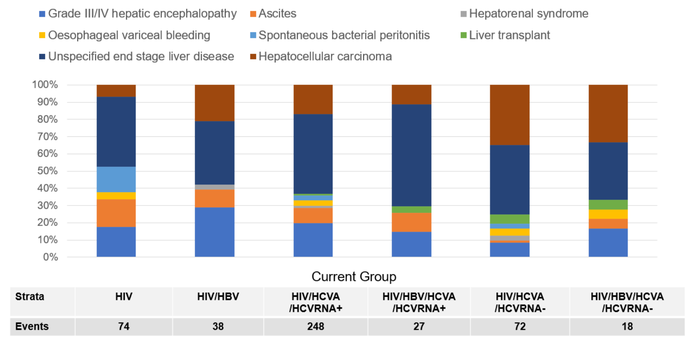
Table 2 : Association between HIV, HBV and HCV strata, ESLD and all-cause mortality

*Incidence rates / 1000 PYFU	HIV	HIV/HBV	HIV/HCVA/ HCVRNA+	HIV/HBV/ HCVA/ HCVRNA+	HIV/HCVA /HCVRNA-	HIV/HBV /HCVA/ HCVRNA-
ESLD						
Events	71	36	237	26	71	17
PYFU	101496	7971	24149	1736	17080	1468
*Incidence (95% CI)	0.7 (0.5–0.9)	4.5 (3.0–6.0)	9.8 (8.6–11.1)	15.0 (9.2–20.7)	4.2 (3.2–5.1)	11.6 (6.8-18.6)
Univariate IRR (95% CI)	0.05 (0.03-0.07)	0.30 (0.18–0.50)	0.66 (0.44–0.98)	1.00 (ref)	0.28 (0.18–0.44)	0.77 (0.42–1.43)
Multivariate IRR* (95% CI)	0.08 (0.05–0.13)	0.45 (0.26–0.77)	0.71 (0.47–1.06)	1.00 (ref)	0.30 (0.19–0.48)	0.85 (0.46–1.57)
All-cause mortality						
Events	1065	119	527	51	229	44
PYFU	101708	8080	24516	1759	17330	1521
*Incidence (95% CI)	10.5 (9.8–11.1)	14.7 (12.1–17.4)	21.5 (19.7–23.3)	29.0 (21.0-37.0)	13.2 (11.5–14.9)	28.9 (20.4–37.5)
Univariate IRR (95% CI)	0.36 (0.27–0.48)	0.51 (0.37–0.71)	0.74 (0.56–0.99)	1.00 (ref)	0.46 (0.34–0.62)	1.00 (0.67–1.49)
Multivariate IRR* (95% CI)	0.49 (0.36–0.66)	0.66 (0.46–0.94)	0.75 (0.56–1.00)	1.00 (ref)	0.54 (0.39–0.73)	1.05 (0.70–1.58)

**ESLD adjusted for gender, HIV transmission category, region of Europe, nadir CD4, age, liver fibrosis stage, and prior ESLD (baseline); smoking, diabetes, CD4 count, HIV viral load, and proportion of follow-up time treated with TDF/TAF+XTC as time-updated variables. All-cause mortality adjusted additionally for ethnicity, prior clinical diagnoses (AIDS, CVD, extrahepatic NADM), and BMI, all fixed at baseline*

**Study group and funding statement at https://chip.dk/Research/Studies/EuroSIDA/Study-group.*

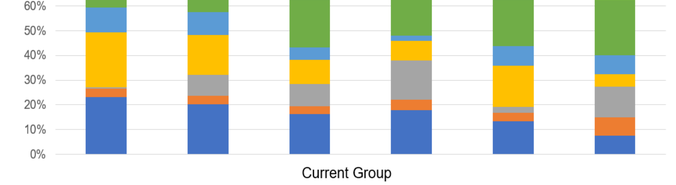
Figure 1 : ESLD, HCC and other liver events by current HBV/HCVA strata



Strata	HIV	HIV/HBV	HIV/HCVA /HCVRNA+	HIV/HBV/HCVA /HCVRNA+	HIV/HCVA /HCVRNA-	HIV/HBV/HCVA /HCVRNA-
Events	74	38	248	27	72	18

All deaths from liver disease included in unspecified end stage liver disease apart from HCC

Figure 2 : Causes of death*



Strata	HIV	HIV/HBV	HIV/HCVA /HCVRNA+	HIV/HBV/HCVA /HCVRNA+	HIV/HCVA /HCVRNA-	HIV/HBV/HCVA /HCVRNA-
Events	1021	118	511	50	203	40

**excluding all deaths during 2019 due to reporting delays. NADM; extrahepatic non AIDS defining malignancy. CVD; cardiovascular disease*

LIMITATIONS

- Not able to adjust for alcohol use or HDV
- Lacked power to look at role of HCV treatment and HBVDNA
- Cannot rule out unmeasured confounding

CONCLUSIONS

- HIV/HBV/HCVA/HCVRNA+ PLWH had higher rates of ESLD and all-cause mortality than those with HIV/HCVA/HCVRNA+.
- After adjustment, the increased rate of ESLD in HIV/HBV/HCVA/HCVRNA+ vs. HIV/HCVA/HCVRNA+ was not statistically significant, possibly due to limited power, but the higher rates for all-cause mortality remained.
- Strategies aimed at ensuring HBV and HCV treatment still need to be prioritized in PLWH with triple infection in Europe
- One of the largest and most heterogenous studies to date including clinically relevant endpoints and HCVRNA data to better define coinfection groups

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References: [1] Duffell EF, EuroSurveillance 2017. [2] Klein MB, AIDS 2014. [3] Nikolopoulos GK, CID 2009.