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P61
Poster for you

HDV co-infection and HCV eradication in persons with HIV (PWH): data from the ICONA cohort

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Italian Cohort I. C. O. N. A. Naive Antiretrovirals
Conceived by Professor Mauro Moroni
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Background

- Direct-acting antivirals (DAA) allow to achieve sustained virological response (SVR) for HCV with high percentage also in people with HIV (PWH)
- Typically, one virus is dominant over the other: dominance occurs when there is inhibition of one viral genome by the other virus
- HBV replication is generally suppressed by viral interference of HCV with consequent risks of HBV reactivation after SVR
- SVR could, therefore, also enhance replication of HDV among triple hepatitis virus co-infected PWH leading to a progression of the underlying liver disease
- Few data are available about the possible role of HBV±HDV co-infections on the outcome of liver disease in PWH who obtained DAA-induced HCV eradication

Aims

1. **To evaluate ALT increase >5 ULN as possible HBV and/or HDV re-activation after HCV eradication**
2. **To evaluate time to ALT normalization, according HBV and HDV co-infections in HIV/HCV individuals who obtained SVR**
3. **To evaluate mean changes in ALT after DAA**

Methods

- **Study Design:** Longitudinal observational cohort study
- **Study population**: HCV co-infected PWH with available HBV serology (HbsAg, HBcAb) enrolled in the Italian ICONA/HepaICONA cohorts who achieved SVR after DAA. In detail the following group were analyzied according to HBV/HDV status
  - **1.** no HBV infection (HBsAg-/HBcAb-)
  - **2.** occult HBV infection (HBsAg- /HBcAb+)
  - **3.** HBV co-infection (HBsAg+)

  HBsAg+ are further stratified based on HDV status
  - **3a.** HbsAg+ /HDVAb+/HDV RNA+
  - **3b.** HbsAg+ /HDVAb+/HDV RNA-
  - **3c.** HbsAg+ /HDVAb+/HDV RNA unknown
  - **3d.** HbsAg+ /HDVAb-
  - **3e.** HbsAg+ /HDVAb unknown
- **Objectives**:
  - Time to ALT normalization (2 consecutive normal ALT values <42 UI/L for males and <30 UI/L for females) after DAA start among those with abnormal values at baseline
  - Time to 2 consecutive ALT values >5x ULN from DAA initiation
  - ALT kinetics after starting DAA
- **Statistical Analysis**: Standard survival analyses and univariate/multivariable Cox regression models were used to estimate time to ALT normalization and time to ALT>5xULN according to HBV/HDV status. Changes of ALT after DAA start according to HBV/HDV status, were evaluated with linear mixed models with random intercept and slopes.

Results

- **1182 HIV/HCV individuals included**:

478 HBsAg neg /HBcAb neg (40.4%)
651 HBsAg neg / HBcAb pos (55.1%)
53 HBsAg pos (4.5%) — **HBV**

→ **21** HDVAb unkwnow (39.6%)
19 HDVAb neg (35.8%)
13 HDVAb pos (24.5%) — **HDV Ab**

→ 6 HDV RNA pos (46.1%)
3 HDV RNA neg (23.1%)
4 HDV RNA unknown (30.8%) — **HDV RNA**

Table 1. Baseline patients' characteristics

		HBV+ N=53 (4.5%)	HBV- N=478 (40.4%)	OBI N=651 (55.1%)	Total N=1,182 (100.0%)	p
Age, median [IQR]		52 [49- 55]	51 [45-55]	54 [50-57]	53 [49-56]	<0.001
Mele sex, n (%)		46 (86.8%)	337 (70.5%)	534 (82.0%)	917 (77.6%)	<0.001
Italian born, n (%)		52 (98.1%)	456 (95.4%)	624 (95.9%)	1,132 (95.8%)	0.640
HIV Risk factor, n (%)	Hetero	6 (11.3%)	90 (18.8%)	52 (8.0%)	148 (12.5%)	<0.001
	IDU	33 (62.3%)	293 (61.3%)	500 (76.8%)	826 (69.9%)	
	MSM	9 (17.0%)	71 (14.9%)	76 (11.7%)	156 (13.2%)	
	Other/Unkn.	5 (9.4%)	23 (5.0%)	23 (3.5%)	52 (4.4%)	
HCV-RNA, log_{10}, UI/ml, median [IQR]		5.93 [5.33-6.37]	5.99 [5.30-6.52]	6.04 [5.44-6.51]	6.00 [6.35-6.50]	0.177
Alcohol use, n (%)	Yes	12 (22.6%)	151 (31.6%)	210 (28.1%)	374 (31.6%)	<.001
	No	10 (18.9%)	167 (34.9%)	258 (39.6%)	435 (36.8%)	
	Unknown	31 (58.5%)	160 (33.5%)	183 (28.1%)	374 (31.6%)	
Diabetes, n (%)		2 (3.8%)	35 (7.3%)	67 (10.3%)	104 (8.8%)	0.092
Bsl. ALT, U/l, median [IQR]		60 [35-103]	57 [37-95]	55 [37-96]	57 [37-96]	<0.001
Bsl. FIB-4, median [IQR]		1.8 [1.2-3.2]	1.5 [1.0-2.3]	1.8 [1.2-2.8]	1.7 [1.2 2.5]	<0.001
FIB-4 class, n (%)	1.45-3.25	18 (36.0%)	186 (39.5%)	290 (45.1%)	494 (42.4%)	<0.001
	<1.45	19 (38.0%)	229 (48.6%)	231 (35.9%)	479 (41.2%)	
	>3.25	13 (26.0%)	56 (11.9%)	122 (19.0%)	191 (16.4%)	
TE liver stiffness, n (%)	F0-F1	12 (26.7%)	185 (48.1%)	234 (41.7%)	431 (43.5%)	<0.001
	F2	4 (8.9%)	84 (21.8%)	105 (18.7%)	193 (19.5%)	
	F3	12 (26.7%)	48 (12.5%)	91 (16.2%)	151 (15.2%)	
	F4	17 (37.8%)	68 (17.7%)	131 (23.4%)	216 (21.8%)	
CD4 cell/mm^3, median [IQR]		604 [419-863]	693 [492-887]	618 [437-868]	648 [452-881]	0.013
HIV-RNA<50 cps/ml, n(%)		49 (94.2%)	438 (93.4%)	612 (94.6%)	1,099 (94.1%)	0.702

ALT >5x ULN

- Figure 1 shows the proportion of PWH with ALT increase >5x UNL in relation with hepatitis status, highest among HBsAg+/HDVRNA+ HIV/HCV individuals (16.7%)
- After adjustments, PWH with HDV co-infection showed a marginally significant higher probability of ALT increase >5x ULN vs HBV- neg (aHR 6.54, 95%CI 0.81-52.8, Table 2)

Figure 1. Proportion of PWH with hepatitic flares (ALT>5xULN) after DAA-start

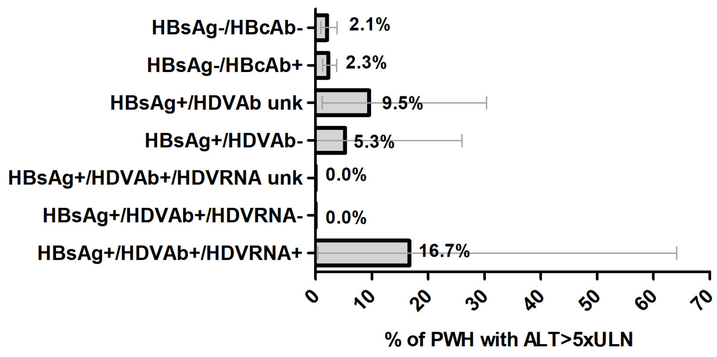


Table 2. Hazard Ratio (HR) and adjusted HR (aHR) of hepatitis flare (ALT>5xULN) according to HBV/HDV status by Cox regression model

	HR	95%CI	p	aHR*	95%CI	p
HBsAg- / HBcAb-	ref			ref		
HBsAg- / HBcAb+	1.12	0.50-2.49	0.79	1.17	0.51-2.70	0.710
HBsAg+ / HDVAb unk	5.81	1.27-26.58	0.02	3.03	0.38-24.07	0.295
HBsAg+ / HDVAb-	2.49	0.32-19.47	0.38	3.31	0.41-26.64	0.261
HBsAg+ / HDVAb+ / HDVRNA unk	.	.	.	.	.	.
HBsAg+/HDVAb+/HDVRNA-	.	.	.	.	.	.
HBsAg+ / HDVAb+ / HDVRNA+	10.21	1.30-79.91	0.03	6.54	0.81-52.82	0.078

**Adjusted for age, sex, baseline FIB4*

ALT normalization

- HBsAg positivity was associated with lower likelihood to normalize ALT (Figure2, log-rank p= 0.044) but, when the HDV co-infection was also included in the Cox model, only for the HCV+ / HBsAg+ / HDVRNA+ group was confirmed (aHR 0.20, 95%CI 0.05-0.82, Table 3)

Figure 2. Kaplan-Meier curves of ALT normalization after DAA start

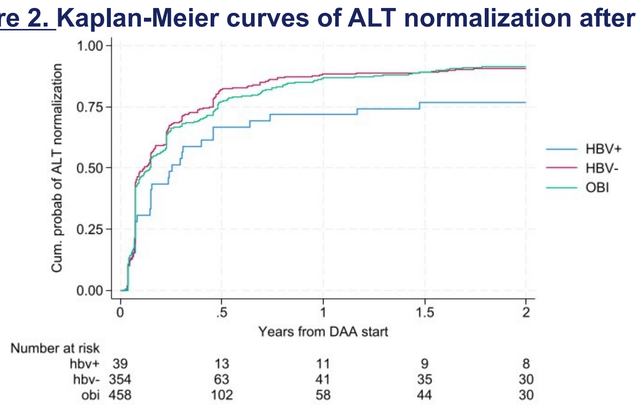


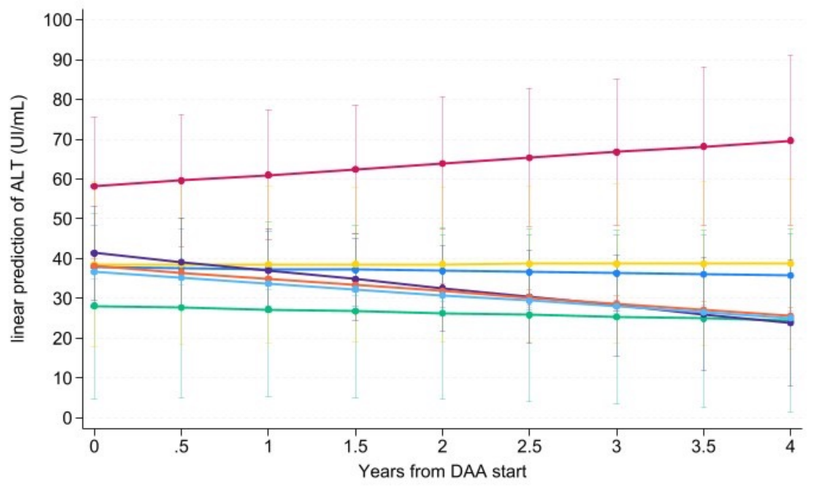
Table 3. HR and aHR of ALT normalization according to HBV/HDV status by Cox regression model

	HR	95%CI	p	aHR*	95%CI	p
HBsAg- / HBcAb-	ref			ref		
HBsAg- / HBcAb+	0.94	0.81-1.08	0.364	0.96	0.83-1.12	0.644
HBsAg+ / HDVAb unk	0.67	0.38-1.2	0.180	0.72	0.38-1.35	0.307
HBsAg+ / HDVAb-	0.89	0.53-1.49	0.646	0.87	0.51-1.49	0.610
HBsAg+ / HDVAb+ / HDVRNA unk	0.31	0.04-2.20	0.241	0.36	0.05-2.6	0.313
HBsAg+/HDVAb+/HDVRNA-	8.95	2.2-36.44	0.002	9.29	2.27-37.95	0.002
HBsAg+ / HDVAb+ / HDVRNA+	0.17	0.04-0.70	0.014	0.20	0.05-0.82	0.025

**Adjusted for age, sex, baseline FIB4*

ALT kinetics

Figure 3. Changes of ALT from DAA start by means of linear mixed models with random intercept and slopes (adjusted for age, sex and baseline FIB4)



	mean ALT change/year	95%CI		p
HBsAg+/HDVAb-	-0.6	-3.0	1.9	0.656
HBsAg+/HDVAb+/HDVRNA+	2.9	-2.3	8.0	0.274
HBsAg+/HDVAb+/HDVRNA-	-0.9	-5.1	3.3	0.665
HBsAg+/HDVAb+/ HDVRNAunk	0.1	-4.0	4.1	0.977
HBsAg+/HDVAbunk	-4.4	-8.8	0.1	0.056
HBsAg-/HBcAb-	-3.1	-3.6	-2.6	<.001
HBsAg-/HBcAb+	-2.9	-3.3	-2.5	<.001

Conclusions

- Almost one fifth of the HIV/HCV individuals with HBV infection of Icona/HepaIcona cohorts were not tested for HDVAb, and 30% of HDVAb+ were not tested for the HDV viral load. In the current scenario with available treatment for HDV it is **essential to identify HDV carriers**
- Our preliminary data demonstrate that PWH with **replicating HDV** infection who achieved HCV eradication show **higher probability of persistent liver necrosis**, as showed by lack of ALT normalization and hepatitis flare after SVR, thus maintaining liver damage.
- Treatment for HDV with **Bulevirtide is mandatory** in this context

Icona Foundation Study Group