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Hepatitis Virus Co-infections and Risk of Diabetes Mellitus and Myocardial Infarction in HIV-infected Persons: The D:A:D Study

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BACKGROUND

Studies among HIV-seronegative individuals have reported a link between hepatitis C virus (HCV) infection and the development of both diabetes mellitus (DM) and myocardial infarction (MI). However, the limited data available in HIV-seropositive populations are conflicting.

METHODS

- D:A:D is a prospective study of 33,347 patients from 11 existing cohorts in Europe, Australia, and the USA
- Using prospective data from the D:A:D cohort, we considered whether hepatitis B (HBV) or C virus (HCV) co-infections were associated with new onset DM or MI
- Follow-up was considered from the time of entry in D:A:D until the earliest of: new onset DM (or MI for analyses of this endpoint); 1st February 2007; death; or six months after the patient's last clinic visit
- Patient follow-up was divided into a series of one-month periods, and each person's HBV/HCV status was determined at the start of each; his/her covariate data was also updated at the start of each month
- Individuals were classified as HCV-seronegative, seropositive or unknown and as HBV-seronegative/vaccinated or having inactive, active (HB surface, HB e antigen, HBV DNA positive) or unknown HBV infection
- Poisson regression assessed the impact of HCV/HBV infection on the development of DM or MI after adjustment for potential confounders (age, sex, risk group, ethnicity, previous AIDS, smoking, family history of cardiovascular disease (CVD), previous CVD, cohort, calendar year, body mass index and exposure to antiretroviral therapy)
- Analyses of MI also controlled for DM development

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Diabetes mellitus 2

Table 1

Comparison of patients who do and do not develop new-onset DM during f/up

		Total	With new DM during f/up	Without DM during f/up
No. of patients		32395	783	31612
Sex	Female	8471 (26.2)	141 (18.0)	8330 (26.4)
Age [years]	Median (IQR)	38 (33-44)	44 (38-52)	38 (33-44)
CD_4 /mm³	Median (IQR)	410 (250-600)	396 (229-586)	410 (250-600)
CD_4 nadir / mm³	Median (IQR)	216 (89-373)	156 (70-299)	218 (90-375)
Weight [kg]	Median (IQR)	70.0 (61.7-78.0)	76.0 (67.0-85.0)	70.0 (61.3-78.0)
BMI [kg/m²]	Median (IQR)	23.0 (21.0-25.2)	25.3 (22.8-27.8)	23.0 (20.9-25.1)
ART status	Naive	8797 (27.2)	143 (18.3)	8654 (27.4)
	Interrupted at baseline	1970 (6.1)	30 (3.8)	1940 (6.1)
	On treatment	21628 (66.8)	610 (77.9)	21018 (66.5)
Exposure to ART, years	Median (IQR)	1.2 (0-2.9)	2.0 (0.1-3.3)	1.2 (0-2.9)
Lipodystrophy	Median (IQR)	5909 (18.2)	242 (30.9)	5667 (17.9)

Table 2

Rates of new-onset DM stratified by latest HCV and HBV status

	New onset DM			
	Events	PYRS	Event rate	95% CI
Overall	783	152054	0.515	0.479 -0.551
HCV status				
Seronegative	462	93335	0.495	0.450 -0.540
Seropositive	178	32090	0.555	0.473 -0.636
Not known	143	26629	0.537	0.449 -0.625
HBV status				
Seronegative	57 0	107994	0.528	0.484 -0.571
Inactive	69	14275	0.483	0.369 -0.597
Active	38	9216	0.412	0.281 -0.543
Unknown	106	20570	0.515	0.417 -0.613

Table 3

Relationship between HCV / HBV status and new-onset DM

	Unadjusted	Adjusted (1)	Adjusted (2)
HCV negative	1	1	1
HCV positive	1.12 (0.94-1.33)	**1.32 (1.04-1.69)***	1.31 (0.97-1.76)
HCV inknown	1.08 (0.90-1.31)	1.02 (0.80-1.30)	1.04 (0.77-1.40)
HBV negative	1	1	1
HBV inactive	0.92 (0.71-1.18)	0.85 (0.65-1.12)	0.92 (0.69-1.24)
HBV active	0.78 (0.56-1.08)	0.74 (0.53-1.02)	0.90 (0.61-1.32)
HBV unknown	0.98 (0.79-1.20)	0.79 (0.59-1.05)	0.89 (0.63-1.25)

*p = 0.02

(1) Adjusted for sex, age, risk, ethnicity, previous AIDS, smoking status, family history of CVD, BMI, cumulative exposure to NRTIs, PIs and NNRTS, cohort and calendar year
(2) As 1 above, + the latest CD_4 count, total- and HDL-cholesterol, triglyceride (log-transformed) values, presence of hypertension and lipodystrophy

Myocardial Infarction

Table 4

Patients who do and do not develop MI

		Total	With new MI during f/up	Without MI during f/up
No. of patients		33347	517	32830
Sex	Female	8655 (26.0)	43 (8.3)	8612 (26.2)
Age [years]	Median (IQR)	38 (33-45)	46 (39-55)	38 (33-44)
CD_4 / mm³	Median (IQR)	408 (248-600)	371 (225-564)	410 (249-600)
CD_4 nadir / mm³	Median (IQR)	214 (88-370)	150 (60-269)	215 (89-372)
Family history of CVD		2250 (6.8)	60 (11.6)	2190 (6.7)
Smoking status	Previous	5617 (16.8)	118 (22.8)	5499 (16.8)
	Current	11316 (33.9)	218 (42.2)	11098 (33.8)
Hypertension		2824 (8.5)	125 (24.2)	2699 (8.2)
Diabetes		852 (2.6)	66 (12.8)	786 (2.4)
Previous CV event		350 (1.1)	51 (9.9)	299 (0.9)
BMI [kg/m2]	Median (IQR)	23.0 (21.0-25.3)	23.4 (21.3-26.1)	23.0 (21.0-25.3)
Exposure to ART [years]	Median (IQR)	1.2 (0-2.9)	2.7 (1.1-3.5)	1.2 (0-2.9)
Total cholesterol	Median (IQR)	4.9 (4.1-5.9)	5.8 (4.9-6.9)	4.9 (4.1-5.8)
HDL colesterol	Median (IQR)	1.1 (0.9-1.4)	1.0 (0.8-1.2)	1.1 (0.9-1.4)
Triglycerides	Median (IQR)	1.6 (1.0-2.6)	2.6 (1.6-3.6)	1.6 (1.0-2.6)
	On lipid-lowering agents	1351 (4.1)	77 (14.9)	1274 (3.9)

Table 5

Rates of new-onset MI stratified by latest HCV and HBV status

	Myocardial infarction			
	Events	PYRS	Event rate	95% CI
Overall	517	157912	0.327	0.299 -0.356
HCV status				
Seronegative	322	96848	0.332	0.296 -0.369
Seropositive	91	33302	0.273	0.217 -0.329
Not known	104	27763	0.375	0.303 -0.447
HBV status				
Seronegative	354	112143	0.316	0.283 -0.349
Inactive	62	14869	0.417	0.313 -0.521
Active	27	9511	0.284	0.177 -0.391
Unknown	74	21389	0.346	0.267 -0.425

Table 6

Relationship between HCV / HBV status and MI

	Unadjusted	Adjusted (1)	Adjusted (2)
HCV negative	1	1	1
HCV positive	0.82 (0.65-1.04)	0.86 (0.62-1.19)	1.14 (0.79-1.66)
HCV unknown	1.13 (0.90-1.41)	0.95 (0.72-1.27)	1.08 (0.78-1.49)
HBV negative	1	1	1
HBV inactive	1.32 (1.01-1.73)	1.07 (0.79-1.43)	1.12 (0.82-1.53)
HBV active	0.90 (0.61-1.33)	0.78 (0.52-1.15)	0.75 (0.47-1.18)
unknown	1.10 (0.85-1.41)	0.96 (0.68-1.36)	0.89 (0.60-1.33)

(1) Adjusted for sex, age, risk, ethnicity, previous AIDS, smoking status, family history of CVD, BMI, cumulative exposure to NRTIs, PIs and NNRTS, cohort and calendar year
(2) As 1 above, + the latest CD_4 count, total- and HDL-cholesterol, triglyceride (log-transformed) values, presence of hypertension and lipodystrophy

RESULTS

- Patient characteristics are summarized in Tables 1 and 4

Diabetes mellitus type 2 (Tables 1-3)

- 783 of 32,395 participants in D:A:D who were free of DM at study entry developed type 2 diabetes mellitus over 152,054 person-years (PY)
- The event rate of DM was 5.15 /1000 PY (95% CI, 4.79, 5.51)
- Event rates in those who were HCV-seronegative and HCV-seropositive were 4.95 (4.50, 5.40) and 5.55 (4.73, 6.36), respectively
- Event rates in those who were HBV-negative or had inactive or active infection were 5.28 (4.84, 5.71), 4.83 (3.69, 5.97) and 4.12 (2.81, 5.43), respectively
- After controlling for potential confounders, HCV-seropositivity was associated with an increased risk of DM: relative rate compared to HCV-seronegative: 1.32 (95% CI, 1.04, 1.69; p = 0.02)
- No similar association was apparent for inactive or active HBV infection
- Further adjustment for changes in lipids had little impact on the results

Myocardial infarction (Tables 4-6)

- 517 patients developed a myocardial infarction over 157,912 PY
- The event rate for MI was 3.27 (95% CI 2.99, 3.56) /1000 PY
- Event rates in those who were HCV-seronegative and HCV-seropositive were 3.32 (2.96, 3.69) and 2.73 (2.17, 3.29), respectively
- Event rates in those who were HBV-negative or had inactive or active infection were 3.16 (2.83, 3.49), 4.17 (3.13, 5.21) and 2.84 (1.77, 3.91), respectively
- After adjustment, there was no relationship between HCV seropositivity, inactive HBV or active HBV infection and the development of MI

CONCLUSIONS

- We found a significant association between HCV (but not HBV) coinfection and the development of new onset type 2 diabetes mellitus
- Pathomechanisms explaining a possible causal relationship between HCV and DM may include: HCV infection (1) causes insulin resistance, insulin deficiency or decreased insulin secretion; (2) directly infects the pancreas or triggers auto-immune β-cell damage; (3) is associated with nonalcoholic fatty liver disease; or (4) generates a „chronic state of inflammation"
- There was no association with HBV and the risk of DM nor between either HCV or HBV coinfection and the development of myocardial infarction
- With the aging of HIV-infected persons due to the success of ART, it is likely that the burden of diabetes mellitus will increase in this population

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