Amager Hvidovre Hospital, Department of Infectious Diseases.
University of Copenhagen, Copenhagen, Denmark

Hepatic steatosis associated with exposure to elvitegravir and raltegravir

0549

Thomas Benfield[1], Jens Lundgren[2], Flemming Bendtsen[3], Susanne Dam Nielsen[4], **Ditte Marie Kirkegaard-Klitbo[1]**; on behalf of the COCOMO study group.

[1]Department of Infectious Diseases, Hvidovre Hospital, University of Copenhagen, Hvidovre, [2]CHIP, Department of Infectious Diseases 8632, Rigshospitalet, University of Copenhagen,[3]Gastrounit, Medical Division, Hvidovre Hospital, University of Copenhagen, Hvidovre, [4]Viro-immunology Research Unit, Department of Infectious Diseases 8632, Rigshospitalet, University of Copenhagen.

BACKGROUND

- Treatment with integrase strand transfer inhibitors and nucleotide analogues may be associated with weight gain in people living with HIV (PWH).
- Overweight is associated with hepatic steatosis.
- Here we studied the association of antiretrovirals and moderate-severe hepatic steatosis.

METHODS

Study population and data collection

PWH aged 40 years and above were recruited from the Copenhagen Co-morbidity (COCOMO) in HIV Infection study in 2015-2016 [1].

We excluded individuals with
- Prior or current hepatitis B or C virus infection
- Self-reported excessive alcohol intake

Clinical and demographic data were collected through physical examinations and blood sampling. Data on antiretroviral therapy were collected from medical records.

Assessment of moderate-to-severe steatosis

Unenhanced CT liver scan was performed on all participants.
A region of interest (ROI) with an area of 1500 mm^2 (+/- 100 mm^2) was placed in Coinaud liver segments 5 and 6 and the average liver attenuation was calculated.
We defined moderate-severe hepatic steatosis as a liver attenuation ≤48 Hounsfield Units (HU) [2].

Statistical analyses

Logistic regression analyses were performed to estimate the association between antiretroviral therapy and moderate-severe hepatic steatosis after adjustment for age, sex, body mass index and HIV duration.

RESULTS

Of 516 PWH, 37 (7.2%) had moderate-severe hepatic steatosis.
The mean treatment duration was 11 years.

Table 1 Clinical and demographic characteristics of PWH (N=516)

Age, median (IQR)	51.0 (43.8, 60.0)
Sex (male), n (%)	445 (86)
Ancestry (Caucasian), n (%)	444 (87)
BMI (kg/m^2), median (IQR)	24.4 (22.2, 27.1)
BMI category (kg/m^2), n (%)	
Underweight, < 18.4	13 (23)
Normoweight, 18.5-24.9	284 (55)
Overweight, 25-29.9	167 (32)
Obese, ≥ 30	50 (10)
Waist circumference, (cm), median (IQR)	93.0 (85, 102)
Diabetes, n (%)	32 (6)
Smoking, n (%)	
Current smoker	140 (27)
Ex smoker	183 (36)
Never smoker	193 (37)
Alcohol (g/week), median (IQR)	60 (12, 96)
Biochemistry, median (IQR)	
ALAT (IU/L)	26.0 (20, 34)
Total cholesterol (mM)	4.8 (4.1, 5.6)
Triglycerides (mM)	1.7 (1.2, 2.7)
Low density lipoprotein (mM)	2.8 (2.2, 3.4)

Abbreviations: PWH: people living with HIV; IQR: interquartile range; BMI: body mass index; ALAT: alanine aminotransferase

Table 2 HIV-specific characteristics of PWH (N=516)

Route of HIV transmission, n (%)	
MSM	371 (73)
HSX	105 (21)
IDU and others	33 (5)
Current CD4 T-cell count (cells/mm^3), median (IQR)	690 (530, 884)
Current CD4 T-cell count > 500 cells/mm^3, n (%)	406 (79)
Nadir CD4 T-cell count (cells/mm^3), median (IQR)	230 (122, 333)
HIV RNA < 50 copies/mL	494 (97)
Duration of HIV infection (years), median (IQR)	14 (7, 22)

Abbreviations: PWH: people living with HIV; IQR: interquartile range; MSM: men sex with men; HSX: heterosexual; IDU: intravenous drug-use

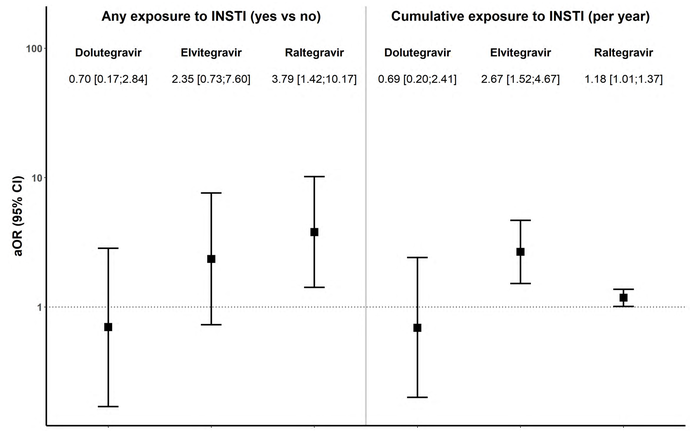

Figure 1. Association between moderate-severe hepatic steatosis and any or cumulative exposure to the integrase inhibitors (INSTI); dolutegravir (N_{exp}=67), elvitegravir (N_{exp}=63) and raltegravir (N_{exp}=59). Model adjusted for age, sex, BMI and duration of HIV infection. Abbreviations: aOR. Adjusted odds ratio; CI:confidence interval.

Any and cumulative exposure to stavudine (N_{exp}=86) was associated with moderate-severe hepatic steatosis (aOR: 2.99 (95% CI: 1.10; 8.16) (yes vs no) and aOR: 1.22 (95% CI: 1.04;1.45) (per year), respectively).

No association was found between moderate-severe hepatic steatosis and any or cumulative exposure to NRTI, NNRTI or protease inhibitors.

CONCLUSION

Moderate-severe hepatic steatosis in PWH without viral hepatitis or excessive alcohol intake was associated with cumulative exposure to stavudine, elvitegravir and raltegravir. Prospective trials are required to establish a causal association.

Acknowledgements: We thank all PLWH and HIV-negative controls for their participation. We thank the staff at Rigshospitalet and Hvidovre Hospital for their dedicated participation.

References: 1. BMC Infect Dis. 2016 Nov 26;16(1):713; **2** Eur Radiol. 2012 May;22(5):1075-82

Correspondence: ditte.marie.kirkegaard-klitbo.01@region.dk