Clinical Infectious Diseases

BRIEF REPORT

Hepatic Steatosis Associated With Exposure to Elvitegravir and Raltegravir

Ditte Marie Kirkegaard-Klitbo,[1] Magda Teresa Thomsen,[2] Marco Gelpi,[2] Flemming Bendtsen,[3,4] Susanne Dam Nielsen,[2,4] and Thomas Benfield,[1,4]; on behalf of the COCOMO study group.

[1]CREDID, Department of Infectious Diseases, Copenhagen University Hospital, Amager and Hvidovre, Hvidovre, Denmark; [2]Viro-immunology Research Unit, Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [3]Gastrounit, Medical Division, Copenhagen University Hospital, Amager and Hvidovre, Hvidovre, Denmark; and [4]Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Moderate-to-severe hepatic steatosis in people living with human immunodeficiency virus (HIV) 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.

Clinical Trials Registration. NCT02382822.

Keywords. NAFLD; HIV; ART.

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the Western World, and people living with human immunodeficiency virus (HIV; PLWH) may be at higher risk. A study by Zelber-Sagi et al found that weight gain was an independent predictor of the development of NAFLD in an HIV-uninfected population [1]. Furthermore, it has become evident that antiretroviral treatment (ART) with integrase strand transfer inhibitors (INSTI) may be associated with weight gain among PLWH [2]. However, the association between INSTI and hepatic steatosis remains to be determined. In this study, we aimed to explore the association between (i) hepatic steatosis and individual antiretroviral agents and (ii) hepatic steatosis and any exposure versus cumulative exposure to ART. This report is an extension of the previous study on hepatic steatosis in HIV infection published by the Copenhagen Co-Morbidity (COCOMO) in HIV Infection Study Group [3].

Received 14 August 2020; editorial decision 19 January 2021; published online 25 January 2021.

Correspondence: D. M. Kirkegaard-Klitbo, Center of Research and Disruption of Infectious Diseases, Department of Infectious Diseases, Hvidovre Hospital, Kettegaard Alle 30, 2650 Hvidovre, Denmark, Europe (ditte.marie.kirkegaard-klitbo.01@regionh.dk).

Clinical Infectious Diseases® 2021;73(3):e811–4

DOI: 10.1093/cid/ciab057

METHODS

Study Population

The COCOMO Study is an observational, prospective cohort study of PLWH in Copenhagen, Denmark [4]. Adult PLWH were consecutively enrolled from March 2015 through November 2016 from the Departments of Infectious Diseases at Rigshospitalet and Amager Hvidovre Hospital. Exclusion criteria for this analysis included prior or current viral hepatitis (positive hepatitis B surface antigen [HBsAg] and/or hepatitis C antibodies [anti-HCV]) and/or alcohol intake above recommendations (>7 units/week for women, >14 units/week for men). The study was approved by the regional ethics committee of the Capital Region of Denmark (record number H-15017350). All participants provided informed consent. The study is registered at clinicaltrials.gov (NCT02382822).

Data Collection

Data on health and lifestyle were collected through comprehensive questionnaires. HIV-specific data and status on hepatitis B virus (HBV) and hepatitis C virus (HCV) infection were collected from medical records. Blood samples were collected from all study participants.

Outcome

Hepatic steatosis was assessed by unenhanced computed tomography (CT) liver scan performed on an Aquillion One scanner (Toshiba Medical Systems, Otawara-shi, Tochigi-ken, Japan) [4, 5]. Liver attenuation was measured using Vitrea 3.1 imaging software (Vital Images Inc., Minnetonka, Minnesota, USA). Moderate-to-severe hepatic steatosis was defined as a CT liver attenuation ≤48 Hounsfield units [6].

Statistical Analysis

Univariable and multivariable logistic regression analyses were conducted with adjustment for age (per decade), sex (male vs female), body mass index (BMI, per 1 kg/m^2), and duration of HIV infection (per year). Results are presented as odds ratios (OR) with 95% confidence intervals (CI). A *P*-value <.05 was considered statistically significant. All analyses were conducted using R version 3.4.1.

RESULTS

A total of 1099 PLWH were included in the COCOMO study. The final study population comprised 516 PLWH after exclusion of individuals due to unavailable CT scan (n = 183), chronic HBV (n = 36), HCV (n = 89), or excessive alcohol intake (n = 209). Clinical and demographic characteristics of the

study population are outlined in Supplementary Tables 1–3. The study population was predominantly male (86%), European (87%), and middle aged (51 years [IQR, 44, 60]). The median BMI was 24.4 kg/m^2 (IQR, 22, 27), and 42% were overweight (BMI >25 kg/m^2). The median weekly alcohol consumption was 5 units for (IQR, 1, 8) and 1 unit (IQR, 0, 3) for women. Approximately half of the study population had dyslipidemia defined as plasma levels of total cholesterol ≥5 mM (46%), triglycerides ≥1.69 mM (52%), LDL >3.0 mM (37%), and HD ≤1.0 mM (47%). The median duration of HIV infection was 14 years (IQR, 6.8, 22), and the majority acquired HIV through homosexual transmission (73%), had an undetectable plasma HIV RNA <20 copies/mL (97%), and a CD4 T-cell count >500 cells/μL (79%). The median nadir CD4 T-cell count was 230 cells/μL (IQR, 122, 332), and 1% had a CD4 T-cell count <200 cells/ μL. The mean treatment duration was 11 years. Moderate-to-severe hepatic steatosis was detected in 37 (7.2%) individuals. In total, 162 (31%) individuals were exposed (N_{exp}) to an INSTI of which 15 (9%) had moderate-to-severe hepatic steatosis. Correspondingly, 67 (13%) individuals were exposed to dolutegravir (DTG), 63 (12%) to elvitegravir (EVG), and 59 (11%) to raltegravir (RAL). Of these, 3 (4%), 6 (10%), and 9 (15%) had moderate-to-severe hepatic steatosis, respectively. Moderate-to-severe hepatic steatosis was associated with any exposure and cumulative exposure (per year) to RAL and with cumulative exposure to EVG (Figure 1). The association with cumulative exposure to EVG with emtricitabine/tenofovir disoproxil fumarate (OR, 3.06 per year [95% CI: 1.63, 5.75]) or with emtricitabine/tenofovir alafenamide (OR, 3.62 per year [95% CI: 0.73, 17.81]) were comparable. No association was found between moderate-to-severe hepatic steatosis and any or cumulative exposure to DTG. Furthermore, moderate-to-severe hepatic steatosis was associated with any exposure to stavudine (OR, 2.10 [95% CI: 1.00, 4.39] and adjusted odds ratio [aOR], 2.99[95% CI: 1.00, 8.16]) and cumulative exposure to stavudine (OR, 1.17 [95% CI: 1.03, 1.32] and aOR, 1.22 [95% CI: 1.02, 1.47] per year) (N_{exp} =86). Test for interaction with stavudine and RAL, and stavudine and EVG were statistically nonsignificant (P = .79 and P = .45, respectively). In sensitivity analysis, plasma levels of triglycerides and presence of diabetes, respectively, were added to the multivariable analysis. The effect of cumulative exposure to EVG attenuated (aOR, 2.60 per year [95% CI: 1.34, 5.07]), although no difference was observed with cumulative exposure to DOL or RAL (Supplementary Table 4).

Any and cumulative exposure (N_{exp}) to abacavir (268), didanosine (78), emtricitabine (263), lamivudine (424), tenofovir disoproxil fumarate (416), tenofovir alafenamide (33), zidovudine (262), efavirenz (338), etravirine (14), nevirapine (113), rilpivirine (25), atazanavir (137), darunavir (135), lopinavir (61), or DTG (67) was not associated with moderate-to-severe hepatic steatosis.

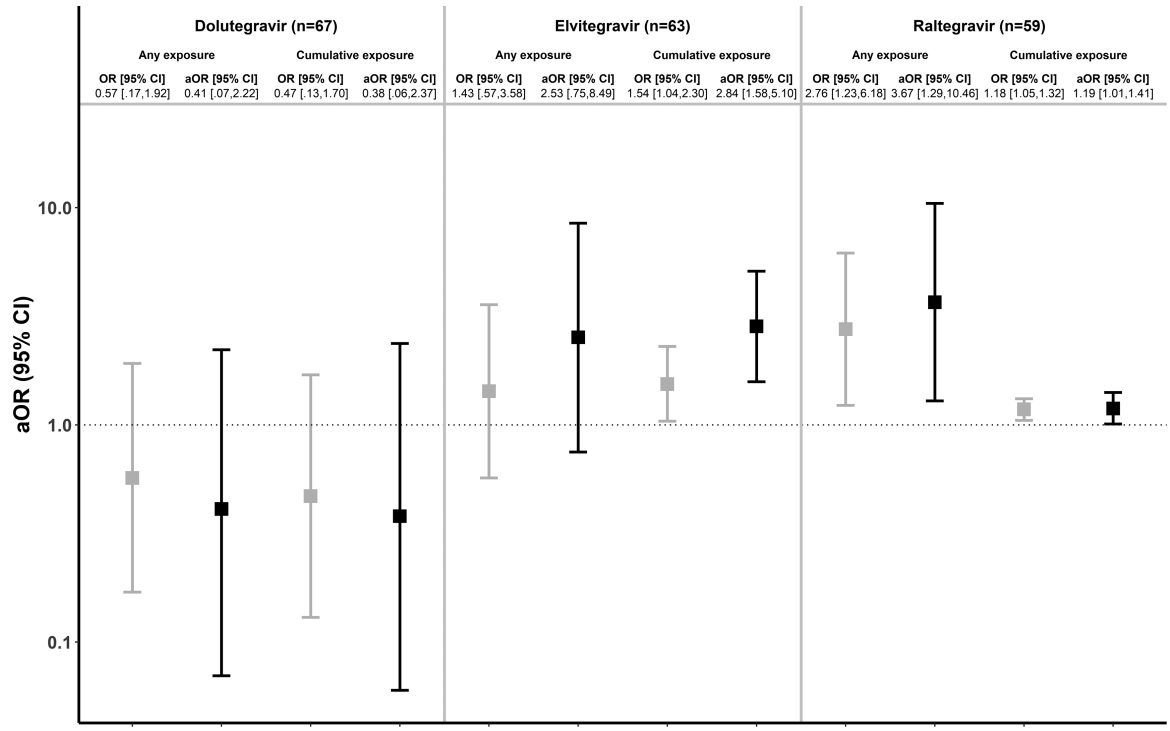

Figure 1. Association between any exposure (yes vs no) and cumulative exposure (per year) of integrase strand transfer inhibitors and moderate-to-severe hepatic steatosis in people living with HIV. Adjustments: sex, age, BMI, and duration of HIV infection. Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

DISCUSSION

In this study of 516 PLWH without viral hepatitis or excessive alcohol intake, exposure to an INSTI and to stavudine were associated with higher odds of moderate-to-severe hepatic steatosis after adjustment for relevant host factors, which is consistent with previous published data from the COCOMO cohort [3]. However, the association was not consistent for all INSTIs. Although exposure to EVG and RAL was associated with higher odds of moderate-to-severe hepatic steatosis, no association was found with exposure to DTG. The association with EVG was consistent regardless of the combination with TDF or TAF, although limited by the small number of individuals exposed to TAF.

INSTI prevent the ongoing HIV replication by inhibition of the HIV DNA integration into the DNA of the $CD4^+$ T cell. Tolerability and a high genetic barrier effect against HIV drug resistance has made an INSTI-based ART regimen the first-line treatment for most PLWH [7]. However, recent studies have reported a greater weight gain in individuals starting INSTI-based therapy compared to protease inhibitor (PI)-based and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy. A study of 22 972 ART-naive PLWH from the North American AIDS Cohort Collaboration on Research and Design showed a gain in weight of 5.9 kg 5 years after initiating INSTI-based ART compared to 5.5 kg for a PI-based regimen and a 3.7 kg for an NNRTI-based regimen [2]. INSTI-associated weight gain differed by drug. The largest weight gain after 2 years of treatment was reported for DTG (7.2 kg), followed by RAL (5.8 kg) and EVG (4.1 kg). The mechanism behind this weight gain has not been clear, but a recent study on human and simian models showed both pro-adipogenic and pro-lipogenic effects of DTG and RAL in addition to oxidative stress, insulin resistance, and mitochondrial dysfunction [8]. In our study, hepatic steatosis was not more prevalent in DTG recipients who may have experienced the highest weight gain and may suggest that the pathogenesis for development of hepatic steatosis are multifactorial. Importantly, we found that a higher BMI was associated with higher odds of hepatic steatosis (aOR, 1.58 per 1 kg/m^2 (95% CI: 1.35, 1.65) and although we adjusted for BMI in the multivariable analysis, residual confounding cannot be precluded [3]. Interestingly, a study by the AIDS Clinical Trials Group A5257 found that RAL recipients experienced a higher increment in waist circumference after 96 weeks of treatment compared to boosted PI recipients [9]. Compared to our results, this suggests that RAL induced increase in waist circumference may play a role in the development of hepatic steatosis by changes in body composition and insulin sensitivity [10].

To our knowledge, this is the first study to link integrase inhibitors with hepatic steatosis. The study has some limitations. Unmeasured residual confounding and channeling bias cannot be excluded, and causality cannot be inferred in a cross-sectional study.

In conclusion, moderate-to-severe hepatic steatosis in PLWH without viral hepatitis or excessive alcohol intake was associated with cumulative exposure to stavudine, EVG, and RAL. Prospective trials are required to establish a causal association of a potential ART-associated hepatic steatosis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgements

We thank all study participants for their participation. We thank all medical staff at the Department of Infectious Diseases, Rigshospitalet and Amager Hvidovre Hospital for their support and participation.

Financial support. This work was supported by Simonsen Foundation, Novo Nordisk Foundation, Lundbeck Foundation, Rigshospitalet Research Council, Region Hovedstaden. Danish National Research Foundation (grant number 126).

Potential conflicts of interest. T. B. reports grants from Pfizer, Novo Nordisk Foundation, Simonsen Foundation, Lundbeck Foundation, and Kai Hansen Foundation; grants and personal fees from GSK, Gilead, and Pfizer; personal fees from Boehringer Ingelheim and MSD, outside the submitted work. S. D. N. reports grants from Novo Nordic Foundation, Rigshospitalet Research Council; and personal fees from Gilead advisory board, GSK advisory board, outside the submitted work. F. B. reports grants from Ferring A/S, and personal fees from Ferring A/S and Norgine, outside the submitted work. All other others report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Zelber-Sagi S, Lotan R, Shlomai A, et al. Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up. J Hepatol **2012**; 56:1145–51.
2. Bourgi K, Jenkins CA, Rebeiro PF, et al.; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Weight gain among treatment-naive persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J Int AIDS Soc **2020**; 23:e25484.
3. Kirkegaard-Klitbo DM, Fuchs A, Stender S, et al. Prevalence and risk factors of moderate to severe hepatic steatosis in HIV infection: the Copenhagen co-morbidity liver study. J Infect Dis **2020**.
4. Ronit A, Haissman J, Kirkegaard-Klitbo DM, et al. Copenhagen comorbidity in HIV infection (COCOMO) study: a study protocol for a longitudinal, non-interventional assessment of non-AIDS comorbidity in HIV infection in Denmark. BMC Infect Dis **2016**; 16:713.
5. Fuchs A, Mejdahl MR, Kühl JT, et al. Normal values of left ventricular mass and cardiac chamber volumes assessed by 320-detector computed tomography angiography in the Copenhagen general population study. Eur Heart J Cardiovasc Imaging **2016**; 17:1009–17.
6. Pickhardt PJ, Park SH, Hahn L, Lee SG, Bae KT, Yu ES. Specificity of unenhanced CT for non-invasive diagnosis of hepatic steatosis: implications for the investigation of the natural history of incidental steatosis. Eur Radiol **2012**; 22:1075–82.
7. Ryom L, Boesecke C, Bracchi M, et al. Highlights of the 2017 European AIDS Clinical Society (EACS) guidelines for the treatment of adult HIV-positive persons version 9.0. HIV Med **2018**; 19:309–15.
8. Gorwood J, Bourgeois C, Pourcher V, et al. The integrase inhibitors dolutegravir and raltegravir exert pro-adipogenic and profibrotic effects and induce insulin

resistance in human/simian adipose tissue and human adipocytes. Clin Infect Dis **2020**.
9. Bhagwat P, Ofotokun I, McComsey GA, et al. Changes in waist circumference in HIV-infected individuals initiating a raltegravir or protease inhibitor regimen: effects of sex and race. Open Forum Infect Dis **2018**; 5:ofy201.
10. Bernardino JI, Mocroft A, Wallet C, et al.; NEAT001/ANRS143 Trial Study Group. Body composition and adipokines changes after initial treatment with darunavir-ritonavir plus either raltegravir or tenofovir disoproxil fumarate-emtricitabine: a substudy of the NEAT001/ANRS143 randomised trial. PLoS One **2019**; 14:e0209911.