MAJOR ARTICLE

Cannabis Use and Reduced Risk of Insulin Resistance in HIV-HCV Infected Patients: A Longitudinal Analysis (ANRS CO13 HEPAVIH)

Maria Patrizia Carrieri,[1,2,3] Lawrence Serfaty,[4] Antoine Vilotitch,[1,2,3] Maria Winnock,[5] Isabelle Poizot-Martin,[6] Marc-Arthur Loko,[5] Caroline Lions,[1,2,3] Caroline Lascoux-Combe,[7] Perrine Roux,[1,2,3] Dominique Salmon-Ceron,[8] Bruno Spire,[1,2,3] and Francois Dabis[5]; for the ANRS CO13 HEPAVIH Study Group[a]

[1]Institut national de la santé et de la recherche médicale (INSERM), Unité mixte de recherche (UMR)912 (Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale [SESSTIM]), [2]Aix Marseille Université, UMR_S912, Institut de recherche pour le développement, and [3]Observatoire Régional de la Santé Provence-Alpes-Côte-d'Azur, Marseille, [4]Service d'hépatologie, Hôpital Saint-Antoine, Assistance publique - Hôpitaux de Paris (APHP), INSERM UMR_938, Université Pierre&Marie-Curie, Paris, [5]INSERM, U897 and Institut de santé publique d'épidémiologie et de développement, Université Victor Segalen, Bordeaux, [6]Aix-Marseille Université, Assistance Publique - Hôpitaux de Marseille Sainte-Marguerite, Service d'Immuno-hématologie Clinique, INSERM U912 (SESSTIM), [7]Hopital Saint-Louis, and [8]Service des Maladies Infectieuses et Tropicales, Hôpital Cochin, APHP-Université Paris Descartes, France

Background. Diabetes and insulin resistance (IR) is common in human immunodeficiency virus–hepatitis C virus (HIV–HCV)-coinfected patients, a population also concerned with elevated cannabis use. Cannabis has been associated with reduced IR risk in some population-based surveys. We determined whether cannabis use was consistently associated with reduced IR risk in HEPAVIH, a French nationwide cohort of HIV–HCV-coinfected patients.

Methods. HEPAVIH medical and sociobehavioral data were collected (using annual self-administered questionnaires). We used 60 months of follow-up data for patients with at least 1 medical visit where IR (using homeostatic model assessment of insulin resistance [HOMA-IR]) and cannabis use were assessed. A mixed logistic regression model was used to evaluate the association between IR risk (HOMA-IR > 2.77) and cannabis use (occasional, regular, daily).

Results. Among the 703 patients included in the study (1287 visits), 323 (46%) had HOMA-IR > 2.77 for at least 1 follow-up visit and 319 (45%) reported cannabis use in the 6 months before the first available visit. Cannabis users (irrespective of frequency) were less likely to have HOMA-IR > 2.77 (odds ratio [95% confidence interval], 0.4 [.2–.5]) after adjustment for known correlates/confounders. Two sensitivity analyses with HOMA-IR values as a continuous variable and a cutoff value of 3.8 confirmed the association between reduced IR risk and cannabis use.

Conclusions. Cannabis use is associated with a lower IR risk in HIV–HCV-coinfected patients. The benefits of cannabis-based pharmacotherapies for patients concerned with increased risk of IR and diabetes need to be evaluated in clinical research and practice.

Keywords. cannabis; insulin resistance; HIV; HCV; cohort study.

Patients with chronic hepatitis C virus (HCV) infection have a higher risk of insulin resistance (IR) and type II diabetes mellitus than patients with other liver diseases. However, it seems that this increased risk of IR is mainly related to HCV infection–related events [1, 2]. One metaanalysis has already shown that pretreatment IR assessment, measured using the homeostasis model assessment of insulin resistance (HOMA-IR), is a major determinant of sustained virological response (SVR) to pegylated-interferon + ribavirin treatment [3]. However, its impact on SVR to telaprevir does not seem significant [4]. The risk of IR and diabetes is even higher in individuals who are coinfected with human immunodeficiency virus (HIV), as a proportion of this population have been exposed to antiretroviral agents (nucleoside/nucleotide

Received 28 November 2014; accepted 9 March 2015; electronically published 16 March 2015.

[a]The Scientific Committee of the ANRS CO13 HEPAVIH Study Group members are listed in the Appendix.

Correspondence: Maria Patrizia Carrieri, PhD, ORS PACA/InsermU912, 23 rue Stanislas Torrents, 13006 Marseille, France (pmcarrieri@aol.com).

Clinical Infectious Diseases® 2015;61(1):40–8

DOI: 10.1093/cid/civ217

reverse transcriptase inhibitors, in particular), which are associated with hyperlipidemia and hypertriglyceridemia [5, 6].

Cannabis use is widespread in France [7], particularly by persons with a history of injecting drug use, who represent a large proportion of the HIV–HCV-infected population. Individuals living with HIV often use cannabis for self-medication, as it helps to reduce the burden of symptoms and ensures adherence to antiretroviral treatment [8, 9]. Although cannabis use can increase appetite, it has been associated with a reduced risk of obesity and therefore IR in the general population [10]. Data that reveal the relationship between cannabis use and both diabetes and IR are sparse. However, a recent cross-sectional study, conducted between 2005 and 2010 in the general US population [11], found that current cannabis use was associated with lower fasting insulin levels and lower risk of IR, highlighted by lower HOMA-IR values and lower risk of diabetes [12].

We used longitudinal data from the Agence nationale de recherches sur le sida et les hépatites virales (ANRS) CO13 HEPAVIH cohort of coinfected HIV–HCV patients to test whether cannabis use in this population, which is particularly concerned with both high prevalence of cannabis use and the risk of IR, was consistently associated with a reduced risk of IR.

MATERIALS AND METHODS

Study Design

In 2006, ANRS CO13 HEPAVIH, a multicenter prospective cohort study, was initiated in 21 infectious diseases and internal medicine outpatient clinics that deliver care to HIV–HCV-coinfected patients in France. Consecutive patients attending 21 hospital wards were enrolled according to the following selection criteria: aged ≥18 years; chronically coinfected with HIV and HCV, as confirmed by a positive HIV antibody test and an HCV RNA assay; or spontaneously cured of HCV without HCV treatment or cured after HCV treatment. Provision of written informed consent was also a condition for enrollment [13].

The institutional review board of Cochin Hospital (Paris) approved the study protocol. The schedule of follow-up visits was based on clinical practice, as recommended by consensus conferences on hepatitis C, ie, every 6 months and every year for cirrhotic and noncirrhotic patients, respectively.

Collection of Biomedical Data

Clinical and biological data, including HIV RNA plasma viral load, CD4 cell count, and degree of liver fibrosis, together with data on HCV treatment initiation, were collected using a clinical research form completed by medical staff in outpatient hospital services. This form also contained other information such as HCV genotype, fibrosis stage, HCV plasma viral load, body mass index (BMI), history of HCV and HIV treatment, fasting glycemia, insulinemia, lipid panel, and comorbidities (such as diabetes, hypertension, cardiovascular problems, renal dysfunction). HIV plasma viral load was considered undetectable if it was below the detection limit (depending on the threshold of the assay used in each outpatient clinic). Although liver biopsy was performed whenever possible at enrollment, a systematic assessment of liver fibrosis was obtained during follow-up using the following 2 noninvasive methods: FibroTest and elastometry by FibroScan. Severe fibrosis (Metavir score F ≥ 3) was assessed using an algorithm that took into account liver biopsy, if available and performed <1 year before the visit; the presence of indirect clinical signs of cirrhosis (esophageal varices, ascites, liver encephalopathy, or digestive bleeding); or results from Fibroscan. The Fibroscan cutoff points used for Metavir score conversion were as follows: F0-F1, <7.1 Kpa; F2, 7.1–9.5 Kpa; F3, 9.5–12.5 Kpa; F4 (cirrhosis), ≥12.5 Kpa [14].

The HOMA-IR was calculated as fasting insulinemia (μU/mL) multiplied by fasting glycemia (mmol/L) divided by 22.5. HOMA-IR is generally used to obtain an indicator of insulin resistance in nondiabetic patients [15]. Further details of medical data collection are documented elsewhere [13].

Patient Self-Administered Questionnaire

The patient self-administered questionnaire was completed at enrollment and during clinical visits every 12 months during the 60 months of follow-up. It detailed sociodemographic characteristics, history of HIV and HCV testing (these 3 only at enrollment), HIV-related symptoms, coffee consumption in the preceding 6 months, and drug (cannabis, heroin, cocaine, crack, ecstasy, street buprenorphine, amphetamines) and alcohol use (AUDIT-C [16]) in the preceding month.

The frequency of consumption of each drug (cannabis, heroin, cocaine, etc.) in the previous 4 weeks was assessed with the following question: Have you used 1 or more of the following drugs in the previous 4 weeks? Possible answers were "never," "sometimes," "regularly," and "every day." Moreover, in order to minimize social desirability bias, information about regular cannabis use was also recorded using a question about regular smoking (cigarettes or other) and recording answers that indicated regular cannabis smoking. Individuals with missing answers or those classified as nonusers or as occasional users as a result of the answer to the first question about cannabis were reclassified as regular cannabis users if they reported regularly smoking cannabis when they answered the second question.

BMI was also computed from participant size and weight data provided at enrollment.

Statistical Methods

Patient Selection

For the statistical analysis, we selected a subset of patients from the HEPAVIH cohort who attended 1 or more follow-up visits where both HOMA-IR and cannabis use (using the HEPAVIH

annual self-administered questionnaire) were assessed. All such visits were included in the analysis. Patients with diabetes at enrollment were excluded from the main analysis, as it was possible they had already changed their lifestyles and were receiving different clinical management. For those patients who developed diabetes during follow-up, only visits before diabetes diagnosis were included in the analysis. Furthermore, visits where HOMA-IR assessments were performed after fasting were excluded from the analysis. However, a sensitivity analysis that included patients with diabetes at baseline and visits of those who developed diabetes during follow-up was conducted to verify the robustness of the results.

Outcomes and Correlates

To compare the distribution of included and excluded patients (Table 1) and the distribution of patient characteristics as a function of cannabis use at first available data (Table 2), a χ^2 test was used for categorical variables. For continuous variables, a Kruskal–Wallis test or Mann–Whitney *U* test was used.

Although controversy about which cutoff values to use to define IR remains [17], we chose a HOMA–IR cutoff value that has already been used in a population without metabolic diseases [18]. This value was also used by Petta et al who found that HOMA-IR >2.7 and platelets <200 × 103/μL were the diagnostic criteria for severe fibrosis (F3 and F4) [19]. The outcome variable was the HOMA-IR measurement, ie, at any given visit, a patient was considered to be at risk of IR if he/she had HOMA-IR values >2.77 at that visit.

To account for the repeated measure design (60-month follow-up) and the presence of fixed (eg, gender) and time-varying correlates, we used a mixed logistic regression model to estimate the adjusted and unadjusted risk of HOMA-IR >2.77 for cannabis use [20].

The following potential correlates/confounders were taken into consideration to test the relationship between cannabis use and HOMA-IR: (1) individual characteristics: age, sex, BMI (<18.5 kg/m^2, 18.5–25 kg/m^2; >25 kg/m^2), and time since enrollment, in years; (2) HIV-related variables: HIV immune-virological status, exposure to specific classes of antiretroviral agents, history of progression to AIDS, CD4 cell count (<200/mm^3; 200–350/mm^3, >350/mm^3), receipt of HIV treatment, injecting drug use HIV transmission category; (3) HCV-related variables: HCV genotype, history of HCV treatment and clearance of HCV at enrollment, cirrhosis (elastometry >12.5 Kpa); and (4) consumption behaviors: drug use (any psychotropic drug use, excluding cannabis), tobacco smoking, alcohol use (elevated alcohol consumption), coffee consumption (3 or more cups per day vs fewer than 3 cups), the former figure corresponding to the value found to be beneficial for liver fibrosis [21], liver enzymes [22], and response to HCV treatment [23]). Variables with *P* values < .20 or known correlates/confounders (eg, coffee consumption) in the univariate analysis were introduced and maintained in the final model if their inclusion significantly improved the model ($P < .05$ for the likelihood ratio test) or if the variable significantly modified the strength of the association between cannabis use and HOMA-IR.

As some research indicates a link between cannabis use and CD4 cell count [24], we conducted a mediation analysis to verify whether the relationship between cannabis use and HOMA-IR could have been mediated by CD4 cell count. Accordingly, we tested the relationship between cannabis use and HOMA-IR, cannabis use and CD4 cell count <350, and CD4 cell count <350 and HOMA-IR [25] using the Sobel test [26]. We also conducted 3 sensitivity analyses. For the first 2, HOMA-IR was considered either as a continuous or dichotomous variable, using a cutoff of 3.8, a value associated with the risk of progression to hepatocellular carcinoma in the same cohort [27]. The third sensitivity analysis used HOMA-IR >2.7 as the outcome included patients who had diabetes at enrollment and visits of those who developed diabetes during follow-up.

Table 1. Characteristics (at Enrollment) of Patients Included In and Excluded From the Analysis

Characteristic	Included (n = 703) N (%) or Median [Interquartile Range]	Excluded (n = 621) N (%) or Median [Interquartile Range]	*P* Value[a]
Gender			
Male	479 (68.1)	349 (73.9)	.04
Female	224 (31.9)	123 (26.1)	
Age at enrollment, years	44 (41–47)	45 (42–48)	.22
Body mass index, kg/m^2			
Underweight	86 (12.3)	53 (11.4)	.04
Normal	499 (71.6)	310 (66.7)	
Overweight/obese	112 (16.1)	102 (21.9)	
CD4 cell count/mm^3			
<200	64 (9.2)	65 (13.9)	.04
200–350	150 (21.5)	103 (21.9)	
>350	483 (69.3)	301 (64.2)	
Human immunodeficiency virus plasma viral load			
Detectable	193 (27.6)	169 (35.8)	$<10^{-2}$
Undetectable	506 (72.4)	303 (64.2)	

[a] χ^2 test for categorical variables or Mann–Whitney *U* test for continuous variables.

RESULTS

Descriptive Results

From the cohort's 1324 HIV–HCV-coinfected patients (7035 visits), 66 (5.0%) had diabetes (I or II) at enrollment and were excluded from the analyses. Among the remaining 1258

Table 2. Characteristics of Patients According to Consumption of Cannabis

Characteristic	Consumption of Cannabis at First Available Data				
	None N = 384	Occasional N = 145	Regular N = 82	Daily N = 92	*P* Value[a]
Gender					
Male	249 (64.8)	107 (73.8)	64 (78.1)	59 (64.1)	.04
Female	135 (35.2)	38 (26.2)	18 (21.9)	33 (35.9)	
Age at enrollment, years	45 (42–48)	44 (42–48)	45 (42–48)	44 (41–47)	.09
Body mass index, kg/m^2					
Underweight	28 (7.6)	23 (16.9)	14 (17.7)	19 (22.6)	$<10^{-3}$
Normal	250 (67.6)	102 (75.0)	58 (73.4)	62 (69.5)	
Overweight	92 (24.8)	11 (8.1)	7 (8.9)	7 (7.9)	
CD4 cell count/mm^3					
<200	33 (8.6)	12 (8.3)	3 (3.7)	5 (5.4)	.59
200–350	76 (19.8)	35 (24.1)	17 (20.7)	22 (23.9)	
>350	275 (71.6)	98 (67.6)	62 (75.6)	65 (70.7)	
HIV plasma viral load					
Detectable	98 (25.7)	32 (22.2)	26 (31.7)	22 (23.9)	.46
Undetectable	284 (74.3)	112 (77.8)	56 (68.3)	71 (76.1)	
Injecting drug use HIV transmission category					
No	158 (42.5)	41 (28.7)	15 (18.5)	10 (11.0)	$<10^{-3}$
Yes	214 (57.5)	102 (71.3)	66 (81.5)	81 (89.0)	
Severe fibrosis (elastometry >12.5 Kpa)					
No	196 (51.0)	68 (46.9)	46 (56.1)	37 (40.2)	.15
Yes	188 (49.0)	77 (53.1)	36 (43.9)	55 (59.8)	
Coffee consumption					
<3 cups/day	295 (77.8)	103 (71.5)	47 (58.8)	59 (64.1)	
≥3 cups/day	84 (22.2)	41 (28.5)	33 (41.2)	33 (35.9)	<.01
Elevated alcohol consumption[b]					
No	338 (91.6)	124 (88.6)	70 (88.6)	81 (88.0)	
Yes	31 (8.4)	16 (11.4)	9 (11.4)	11 (12.0)	.59

Abbreviations: AU, alcohol unit; HIV, human immunodeficiency virus.

[a] χ^2 test for categorical variables or Kruskal–Wallis test for continuous variables.

[b] ≥90 AU per month for men, ≥60 AU per month for women.

patients (6270 visits), 947 and 1021 had at least 1 follow-up visit with data on cannabis use and HOMA-IR, respectively. In addition, 813 patients (65%), corresponding to 1580 visits, had data on both cannabis use and HOMA-IR at a minimum of 1 follow-up visit. Among the latter, 110 had fasted before the HOMA-IR assessment and were excluded. Among the other 703, 5 (incidence rate = 0.36 per 100 person-years) were clinically diagnosed with diabetes during follow-up, and so only visits before their diagnosis were included in the analysis.

Compared with excluded patients (N = 621), patients included in the analysis (N = 703) were more likely to be female and to have an undetectable viral load, higher CD4 cell count, and normal BMI (Table 1). Among the 703 patients included in this analysis, 323 (46%) and 212 (30%) had a HOMA-IR >2.77 and a HOMA-IR >3.8 at 1 or more follow-up visits, respectively.

At their first visit with available data, 384 (54.6%) patients reported no use of cannabis in the previous 4 weeks, while 145 (20.6%), 82 (11.7%), and 92 (13.1%) patients reported occasional, regular, and daily use, respectively. The median (interquartile range [IQR]) HOMA-IR value was 2.06 (1.42;3.36).

Median [IQR] age was 45 [42–48] years and 479 were men. The percentage of patients with genotypes 1, 2, 3, 4, and 5 was 55.6%, 3.2%, 18.5%, 22.4%, and 0.3%, respectively. The percentage of patients with BMI > 27 kg/m^2 was 17.4%. A significant association was found between BMI and cannabis use (Table 2).

Univariate Analysis

Unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the potential correlates of HOMA-IR >2.77 are reported in Table 3. The univariate analysis (Table 3) showed that cannabis use (whether occasional, regular, or daily) was significantly

Table 3. Potential Correlates/Confounders of the Risk of Insulin-Resistance (Homeostatic Model Assessment of Insulin Resistance >2.77): Crude Odds Ratios and Their 95% Confidence Intervals, Estimated by Mixed Logistic Regression Model (N = 703 Patients; 1287 Visits) in the ANRS CO13 HEPAVIH Cohort

Correlates and Confounders	No. Visits (%) or Median (Interquartile Range) (n = 1287)	No. Patients N (%; n = 703)[a]	Homeostatic Model Assessment of Insulin Resistance >2.77 Odds Ratio (95% Confidence Interval)	*P* Value
Gender				
Male	874 (67.9)	479 (68.1)	1	
Female	413 (32.1)	224 (31.9)	0.5 (.3–.7)	$<10^{-2}$
Age, years	46 (42–49)		1.04 (1.00–1.07)	.03
Time since enrollment, years			1.04 (.94–1.15)	.43
Body mass index, kg/m^2	1 (0–2)			
Underweight	148 (12.9)	105 (15.6)	0.5 (.3–.9)	.03
Normal	778 (67.8)	492 (72.9)	1	
Overweight/Obese	222 (19.3)	139 (20.6)	4.1 (2.4–7.0)	$<10^{-3}$
CD4 cell count/mm^3				
<200	83 (6.5)	69 (9.8)	2.0 (1.0–4.1)	.06
200–350	260 (20.2)	205 (29.2)	1.6 (1.0–2.5)	.03
>350	944 (73.3)	547 (77.8)	1	
HIV plasma viral load				
Detectable	287 (22.5)	218 (31.1)	0.7 (.5–1.1)	.10
Undetectable	991 (77.5)	588 (83.9)	1	
Previous exposure to D4T				
No	480 (37.3)	261 (37.1)	1	
Yes	807 (62.7)	442 (62.9)	1.6 (1.1–2.5)	.03
History of progression to AIDS				
No	908 (70.7)	501 (71.5)	1	
Yes	377 (29.3)	202 (28.8)	1.3 (.8–2.1)	.21
Receiving HIV treatment				
Yes	1244 (98.0)	682 (98.6)	1	
No	25 (2.0)	19 (2.8)	0.5 (.1–1.9)	.29
Injecting drug use HIV transmission category				
No	434 (34.2)	244 (35.0)	1	
Yes	837 (65.8)	479 (68.7)	1.0 (.6–1.5)	.90
Hepatitis C virus clearance at enrollment				
Yes	136 (10.6)	81 (11.5)	1	
No	1151 (89.4)	622 (88.5)	1.5 (.8–3.1)	.22
Cirrhosis (elastometry >12.5 Kpa)				
No	646 (50.1)	430 (61.2)	1	
Yes	641 (40.9)	456 (64.9)	1.9 (1.3–2.6)	$<10^{-3}$
Elevated alcohol consumption[b]				
No	1136 (91.3)	639 (92.6)	1	
Yes	108 (8.7)	78 (11.3)	0.7 (.3–1.3)	.24
Consumption of cannabis				
No	739 (57.4)	434 (61.7)	1	
Occasional	239 (18.6)	177 (25.2)	0.3 (.2–.5)	$<10^{-3}$
Regular not daily	146 (11.3)	113 (16.1)	0.3 (.2–.6)	$<10^{-2}$
Daily	163 (12.7)	120 (17.1)	0.4 (.2–.7)	$<10^{-2}$
Consumption of cannabis				
No	739 (57.4)	434 (61.7)	1	
Yes	548 (42.6)	345 (49.1)	0.3 (.2–.5)	$<10^{-3}$

Table 3 continued.

Correlates and Confounders	No. Visits (%) or Median (Interquartile Range) (n = 1287)	No. Patients N (%; n = 703)[a]	Homeostatic Model Assessment of Insulin Resistance >2.77 Odds Ratio (95% Confidence Interval)	*P* Value
Coffee consumption				
<3 cups/day	921 (73.1)	548 (78.5)	1	
≥3 cups/day	339 (26.9)	225 (32.2)	0.6 (.4–1.0)	.03

Abbreviations: AU, alcohol unit; HIV, human immunodeficiency virus.

[a] The percentages computed in this column do not add up to 100% as each percentage refers to the proportion of individuals who presented the characteristics at least once during follow-up.

[b] ≥90 AU per month for men, ≥60 AU per month for women.

associated with lower risk of IR. As ORs of any cannabis use category (vs no use) were very similar (Table 3) and did not change after multiple adjustments, we decided to collapse the 3 categories of cannabis use. Drinking 3 or more cups of coffee per day was also found to be a significant correlate of reduced risk of IR.

Compared with men, women had approximately half the risk of having IR. No significant association was found between HCV genotype and IR (data not shown). Detectable HIV viral load was associated with a reduced risk of IR. All HIV antiretrovirals were tested for, but only exposure to D4T was significantly associated with an increased risk of IR.

Individuals with cirrhosis had at least a 50% higher risk of having IR.

In the mediation analyses, the Sobel test was not significant, thereby confirming no significant mediation effect by CD4 cell count in the relationship between cannabis use and HOMA-IR.

Multivariate Analysis

The relationship between cannabis use and reduced risk of IR was confirmed after adjustment for gender, immunovirological status, exposure to D4T, BMI, HCV clearance at enrollment, elevated coffee consumption, and cirrhosis (Table 4). Age was neither a independent significant correlate nor a confounder and was not included in the final model. A second model was built (model 2, Table 4) by removing cirrhosis from model 1, as it was collinear with low coffee consumption. In model 2, elevated coffee consumption was independently associated with lower risk of IR.

Sensitivity analyses confirmed the association with cannabis use (yes vs no) when using a HOMA-IR cutoff value of 3.8 (OR [95% CI], 0.4 [.2–.6]; $P < 10^{-3}$) or using continuous values of HOMA-IR (coefficient [95% CI], −0.6 [−.9;−.4]; $P < 10^{-3}$) after adjustment for a similar pattern of significant predictors. The third sensitivity analysis, which used HOMA-IR >2.77 and also included patients with diabetes, confirmed the significant association between cannabis use and the reduced risk of IR (OR [95% CI], 0.4 [.2–.6]; $P < 10^{-3}$) after adjustment for the same pattern of independent predictors.

DISCUSSION

This is the first longitudinal study to document the relationship between the reduced risk of IR and cannabis use in a population

Table 4. Factors Independently Associated With Homeostatic Model Assessment of Insulin Resistance >2.77 (Multivariate Logistic Mixed Model, N = 669 Individuals, N = 1121 Visits)

	Model 1		Model 2[a]	
	HOMA-IR >2.77		HOMA-IR >2.77	
Correlates and Confounders	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Sex				
Male	1		1	
Female	0.5 (.3–.8)	$<10^{-2}$	0.4 (.3–.7)	$<10^{-2}$
Body mass index, kg/m^2				
Underweight	0.5 (.3–1.0)	.05	0.5 (.3–1.0)	.04
Normal	1		1	
Overweight/Obese	3.0 (1.8–5.2)	$<10^{-3}$	3.2 (1.8–5.5)	$<10^{-2}$
Human immunodeficiency virus viral load				
Detectable	0.6 (.4–1.0)	.03	0.6 (.4–1.0)	.04
Undetectable	1		1	
Previous exposure to D4T				
No	1		1	
Yes	1.7 (1.1–2.6)	.02	1.8 (1.1–2.9)	.01
Cirrhosis (elastometry >12.5 Kpa)				
No	1			
Yes	1.8 (1.3–2.6)	$<10^{-2}$		
Consumption of cannabis				
No	1		1	
Yes	0.4 (.2–.5)	$<10^{-3}$	0.4 (.2–.6)	$<10^{-3}$
Coffee consumption				
<3 cups/day			1	
≥3 cups/day			0.6 (.4–1.0)	.05

Abbreviations: CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; OR, odds ratio.

[a] In model 2, cirrhosis was removed as it was collinear with elevated coffee consumption.

particularly concerned with IR risk. The results were robust, as they were confirmed in 3 sensitivity analyses; 1 of these analyses included patients with diabetes.

Our results are consistent with those from previous research [12] and, in particular, with a recent cross-sectional study conducted in the US general population [11]. In our study, cannabis users were more likely to have a low BMI, which is in line with previous research [10]. As a high BMI is also associated with increased risk of diabetes, it was necessary to adjust for BMI in the final model in order to determine whether the relationship between cannabis use and IR could be confirmed. The associations we found among cannabis use, obesity, and reduced risk of IR are also consistent with results from animal models. When administered to obese rats, cannabis was associated with weight reduction and an increase in the weight of the pancreas, implying beta-cell protection [28].

The mechanisms by which cannabinoids affect peripheral metabolism via type 1 and 2 cannabinoid receptors have been extensively studied [29]. Nevertheless, the causal link is not completely understood. Evidence is emerging that some nonpsychotropic plant cannabinoids, such as cannabidiol, can be used to retard beta-cell damage in type I diabetes [29]. For example, mice models suggest that rimonabant, the cannabinoid type 1 receptor antagonist, can improve insulin sensitivity and that this effect is mediated by adiponectin [30]. However, a recent study in adiponectin knockout mice showed that improvement of insulin sensitivity in obese mice on rimonabant is independent of adiponectin [31]. Another recent study by Muniyappa et al [32] shows that chronic cannabis use increases adipocyte IR without affecting glucose insulin sensitivity. It is therefore difficult to say whether or not the association found in our study is attributable to this adiponectin-mediated mechanism. Moreover, such a mechanism (ie, modification of adiponectin levels) has also been documented for coffee intake [33]. The association we found between elevated coffee consumption and reduced risk of IR is also consistent with a relationship found in the same cohort using cross-sectional enrollment data [22] and that found in a very recent study in a large cohort of health staff [34]. Previous studies have already shown that several combined effects of coffee components (chlorogenic acid, in particular) may have different consequences, including the regulation of hormones involved in satiety and insulin secretion [35].

Individuals who presented with HIV viral replication were at lower risk of IR in our study, perhaps because this variable is a proxy of no or suboptimal exposure to antiretroviral treatment, not of virological failure. Among all antiretroviral agents tested, only exposure to stavudine (D4T) remained statistically significant in the final model, confirming previous results that showed that cumulative exposure to stavudine predicts IR [5] and diabetes [36] in HIV-infected individuals. As highlighted by Loko et al [6], the mechanism that links exposure to specific antiretroviral agents, IR, and liver fibrosis is complex and is mediated by mitochondrial toxicity.

Some limitations of this study need to be acknowledged. First, the assessment of cannabis use was based on self-reports. Accordingly, social desirability bias may have resulted in underreporting of such behaviors. Second, there is no gold standard for the cutoff values for HOMA-IR, and we preferred to use those indicated for patients with no diabetes and genotype 1 [17, 19] in order to obtain a more sensitive measure of IR. However, the use of a more "specific" (higher) cutoff value and measurement of the outcome as a continuous variable in the sensitivity analyses confirmed the association between cannabis use and reduced IR risk. Third, the generalization of our findings may be limited by the exclusion of individuals who did not answer the self-administered questionnaire and who exhibited poorer immunological status than those included in the analysis. Nevertheless, because the French healthcare system guarantees free access to HIV and HCV care for all patients, the HEPAVIH cohort is likely to include a higher proportion of underprivileged populations than most clinical trials or other longitudinal studies carried out in countries where such access is not available.

There are several cannabis-based pharmacotherapies that do not rely on herbal marijuana and are used for specific indications (eg, symptoms relief in multiple sclerosis). The benefits of these products for patients concerned with increased risk of IR and diabetes need to be evaluated in clinical research and practice.

Notes

Acknowledgments. We thank all members of the Agence nationale de recherches sur le sida et les hépatites virales (ANRS) CO13 HEPAVIH study group. We especially thank all the physicians and nurses who are involved in the follow-up of the cohort and all patients who took part in this study. Finally, we thank Jude Sweeney for the English revision and editing of our manuscript.

Disclaimer. The funding source had no involvement in any element of this paper.

Financial support. This work was supported by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS), Abbott France; Glaxo-Smith-Kline, Roche; Schering-Plough, and Institut national de la santé et de la recherche médicale's Programme Cohortes TGIR.

Potential conflicts of interest. L. S. discloses consulting and participation in advisory committees in addition to review panels for the following companies: Abbvie, Janssen, Merck Sharp & Dohme, Roche, Bristol–Meyers Squibb (BMS), Gilead, GlaxoSmithKline (GSK), and Aptalis. D. S.-C. discloses invited seminars and physician training funded by BMS, GSK, Diasorin, Merck, and Janssen. All other authors 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. Bugianesi E, Salamone F, Negro F. The interaction of metabolic factors with HCV infection: does it matter? J Hepatol **2012**; 56(Suppl 1): S56–65.

2. Pattullo V, Heathcote J. Hepatitis C and diabetes: one treatment for two diseases? Liver Int **2010**; 30:356–64.
3. Deltenre P, Louvet A, Lemoine M, et al. Impact of insulin resistance on sustained response in HCV patients treated with pegylated interferon and ribavirin: a meta-analysis. J Hepatol **2011**; 55:1187–94.
4. Serfaty L, Forns X, Goeser T, et al. Insulin resistance and response to telaprevir plus peginterferon alpha and ribavirin in treatment-naive patients infected with HCV genotype 1. Gut **2011**; 61:1473–80.
5. Brown TT, Li X, Cole SR, et al. Cumulative exposure to nucleoside analogue reverse transcriptase inhibitors is associated with insulin resistance markers in the Multicenter AIDS Cohort Study. AIDS **2005**; 19: 1375–83.
6. Loko MA, Bani-Sadr F, Winnock M, et al. Impact of HAART exposure and associated lipodystrophy on advanced liver fibrosis in HIV/HCV-coinfected patients. J Viral Hepat **2011**; 18:e307–14.
7. Observatoire français des drogues et des toxicomanies. Estimation du nombre de consommateurs de cannabis en France métropolitaine parmi les 11–75 ans en 2011. Available at: http://www.ofdt.fr/ofdtdev/live/produits/cannabis/conso.html. Accessed 27 November 2014.
8. Cinti S. Medical marijuana in HIV-positive patients: what do we know? J Int Assoc Physicians AIDS Care (Chic) **2009**; 8:342–6.
9. de Jong BC, Prentiss D, McFarland W, Machekano R, Israelski DM. Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea. J Acquir Immune Defic Syndr **2005**; 38:43–6.
10. Le Strat Y, Le Foll B. Obesity and cannabis use: results from 2 representative national surveys. Am J Epidemiol **2011**; 174:929–33.
11. Penner EA, Buettner H, Mittleman MA. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. Am J Med **2013**; 126:583–9.
12. Rajavashisth TB, Shaheen M, Norris KC, et al. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. BMJ Open **2012**; 2: e000494.
13. Loko MA, Salmon D, Carrieri P, et al. The French national prospective cohort of patients co-infected with HIV and HCV (ANRS CO13 HEPAVIH): early findings, 2006–2010. BMC Infect Dis **2010**; 10:303–13.
14. Castera L, Le Bail B, Roudot-Thoraval F, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J Hepatol **2009**; 50:59–68.
15. Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care **2000**; 23:57–63.
16. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med **1998**; 158:1789–95.
17. Eslam M, Kawaguchi T, Del Campo JA, Sata M, Khattab MA, Romero-Gomez M. Use of HOMA-IR in hepatitis C. J Viral Hepat **2011**; 18: 675–84.
18. Bonora E, Kiechl S, Willeit J, et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. Diabetes **1998**; 47:1643–9.
19. Petta S, Camma C, Di Marco V, et al. Hepatic steatosis and insulin resistance are associated with severe fibrosis in patients with chronic hepatitis caused by HBV or HCV infection. Liver Int **2011**; 31:507–15.
20. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. Stat Med **1997**; 16:2349–80.
21. Saab S, Mallam D, Cox Ii GA, Tong MJ. Impact of coffee on liver diseases: a systematic review. Liver Int **2014**; 34:495–504.
22. Carrieri MP, Sogni P, Cohen J, Loko MA, Winnock M, Spire B. Elevated coffee consumption and reduced risk of insulin resistance in HIV-HCV coinfected patients (HEPAVIH ANRS CO-13). Hepatology **2012**; 56:2010.
23. Freedman ND, Curto TM, Lindsay KL, Wright EC, Sinha R, Everhart JE. Coffee consumption is associated with response to peginterferon and ribavirin therapy in patients with chronic hepatitis C. Gastroenterology **2011**; 140:1961–9.
24. Costantino CM, Gupta A, Yewdall AW, Dale BM, Devi LA, Chen BK. Cannabinoid receptor 2-mediated attenuation of CXCR4-tropic HIV infection in primary CD4+ T cells. PloS One **2012**; 7:e33961.
25. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol **1986**; 51:1173–82.
26. Sobel ME. Asymptotic intervals for indirect effects in structural equation models. Sociol Methodol **1982**; 13:290–312.
27. Salmon D, Bani-Sadr F, Loko MA, et al. Insulin resistance is associated with a higher risk of hepatocellular carcinoma in cirrhotic HIV/HCV-co-infected patients: results from ANRS CO13 HEPAVIH. J Hepatol **2012**; 56:862–8.
28. Levendal RA, Schumann D, Donath M, Frost CL. Cannabis exposure associated with weight reduction and beta-cell protection in an obese rat model. Phytomedicine **2012**; 19:575–82.
29. Di Marzo V, Piscitelli F, Mechoulam R. Cannabinoids and endocannabinoids in metabolic disorders with focus on diabetes. Handb Exp Pharmacol **2011**; 203:75–104.
30. Migrenne S, Lacombe A, Lefevre AL, et al. Adiponectin is required to mediate rimonabant-induced improvement of insulin sensitivity but not body weight loss in diet-induced obese mice. Am J Physiol Regul Integr Comp Physiol **2009**; 296:R929–35.
31. Tam J, Godlewski G, Earley BJ, et al. Role of adiponectin in the metabolic effects of cannabinoid type 1 receptor blockade in mice with diet-induced obesity. Am J Physiol Endocrinol Metab **2014**; 306:E457–68.
32. Muniyappa R, Sable S, Ouwerkerk R, et al. Metabolic effects of chronic cannabis smoking. Diabetes Care **2013**; 36:2415–22.
33. de Oliveira C, de Mattos AB, Silva CB, Mota JF, Zemdegs JC. Nutritional and hormonal modulation of adiponectin and its receptors adipoR1 and adipoR2. Vitam Horm **2012**; 90:57–94.
34. Bhupathiraju SN, Pan A, Manson JE, Willett WC, van Dam RM, Hu FB. Changes in coffee intake and subsequent risk of type 2 diabetes: three large cohorts of US men and women. Diabetologia **2014**; 57:1346–54.
35. Tunnicliffe JM, Shearer J. Coffee, glucose homeostasis, and insulin resistance: physiological mechanisms and mediators. Appl Physiol Nutr Metab **2008**; 33:1290–300.
36. De Wit S, Sabin CA, Weber R, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Diabetes Care **2008**; 31:1224–9.

APPENDIX

Scientific Committee of the ANRS CO13 HEPAVIH Study Group

D. Salmon and F. Dabis (principal investigators), M. Winnock, M.-A. Loko, P. Sogni, Y. Benhamou, P. Trimoulet, J. Izopet, V. Paradis, B. Spire, P. Carrieri, C. Katlama, G. Pialoux, M. A. Valantin, P. Bonnard, I. Poizot-Martin, B. Marchou, E. Rosenthal, D. Garipuy, O. Bouchaud, A. Gervais, C. Lascoux-Combe, C. Goujard, K. Lacombe, C. Duvivier, D. Vittecoq, D. Neau, P. Morlat, F. BaniSadr, L. Meyer, F. Boufassa, S. Dominguez, B. Autran, A. M. Roque, C. Solas, H. Fontaine, L. Serfaty, G. Chêne, D. Costagliola, D. Zucman, A. Simon, S. Dominguez,

E. Billaud, P. Miailhes, J. Polo Devoto, S. Couffin-Cadiergues (Agence nationale de recherches sur le sida et les hépatites virales [ANRS]).

Clinical Centers (Ward/Participating Physicians). Cente hospitalier universitaire (CHU) Cochin (Médecine Interne et Maladies Infectieuses/D. Salmon, H. Mehawej; Hépato-gastro-entérologie/P. Sogni; Anatomo-pathologie/B. Terris, Z. Makhlouf, G. Dubost, F. Tessier, L. Gibault, F. Beuvon, E. Chambon, T. Lazure; Virologie/A. Krivine. CHU Pitié-Salpétrière (Maladies Infectieuses et Tropicales/C. Katlama, M. A. Valantin, H. Stitou; Hépato-gastro-entérologie/Y. Benhamou; Anatomo-pathologie/F. Charlotte; Virologie/S. Fourati). CHU Pitié-Salpétrière (Médecine Interne/A. Simon, P. Cacoub, S. Nafissa; Anatomo-pathologie/F. Charlotte; Virologie/S. Fourati). CHU Sainte-Marguerite, Marseille (Service d'Immuno-Hématologie Clinique-Centre d'Information et de Soins de l'Immunodéficience Humaine/I. Poizot-Martin, O. Zaegel, A. Ménard, P. Geneau; Virologie/C. Tamalet). CHU Tenon (Maladies Infectieuses et Tropicales/G. Pialoux, P. Bonnard, F. Bani-Sadr, L. Slama, T. Lyavanc; Anatomo-pathologie/P. Callard, F. Bendjaballah; Virologie/C. Le-Pendeven). CHU Purpan Toulouse (Maladies Infectieuses et Tropicales/B. Marchou; Hépato-gastro-entérologie/L. Alric, K. Barange, S. Metivier, A. Fooladi; Anatomo-pathologie/J. Selves; Virologie/F. Nicot). CHU Archet, Nice (Médecine Interne/E. Rosenthal; Infectiologie/J. Durant; Anatomo-pathologie/J. Haudebourg, M. C. Saint-Paul). CHU Avicenne, Paris (Médecine Interne–Unité Virus de l'Immunodéficience Humaine/O. Bouchaud; Anatomo-pathologie/M. Ziol; Virologie/Y. Baazia). Hôpital Joseph-Ducuing, Toulouse (Médecine Interne/M. Uzan, A. Bicart-See, D. Garipuy, M. J. Ferro-Collados; Anatomo-pathologie/J. Selves; Virologie/F. Nicot). CHU Bichat–Claude-Bernard, Paris (Maladies Infectieuses/P. Yéni, A. Gervais; Anatomo-pathologie/H. Adle-Biassette). CHU Saint-Louis (Maladies Infectieuses/J. M. Molina, C. Lascoux-Combe; Anatomo-pathologie/P. Bertheau, J. Duclos; Virologie/P. Palmer). CHU Saint Antoine (Maladies Infectieuses et Tropicales/P. M. Girard, K. Lacombe, P. Campa; Anatomo-pathologie/D. Wendum, P. Cervera, J. Adam; Virologie/N. Harchi). CHU Bicêtre (Médecine Interne/J. F. Delfraissy, C. Goujard, Y. Quertainmont; Virologie/C. Pallier). CHU Paul-Brousse (Maladies Infectieuses/D. Vittecoq). CHU Necker (Maladies Infectieuses et Tropicales/O. Lortholary, C. Duvivier, M. Shoai-Tehrani), ANRS CO 3 Aquitaine Cohort (D. Neau, P. Morlat, L. Lacaze-Buzy, S. Caldato; Anatomo-pathologie/P. Bioulac-Sage; Virologie/P. Trimoulet, S. Reigadas). Hôpital FOCH, Suresnes (Médecine Interne/D. Zucman, C. Majerholc; Virologie/F. Guitard). CHU Antoine Béclère (Médecine Interne/F. Boue, J. Polo Devoto, I. Kansau, V. Chambrin, C. Pignon, L. Berroukeche, R. Fior, V. Martinez; Virologie/C. Deback). CHU Henri Mondor (Immunologie Clinique/Y. Lévy, S. Dominguez, J. D. Lelièvre, A. S. Lascaux, G. Melica). CHU Hôtel Dieu, Nantes (Maladies Infectieuses et Tropicales/F. Raffi, E. Billaud, C. Alavena; Virologie/A. Rodallec). Hôpital de la Croix Rousse, Lyon (D. Peyramond, C. Chidiac, P. Miailhes, F. Ader, F. Biron, A. Boibieux, L. Cotte, T. Ferry, T. Perpoint, J. Koffi, F. Zoulim, F. Bailly, P. Lack, M. Maynard, S. Radenne, M. Amiri; Virologie/Le-Thi Than-Thuy).

Data Collection, Management, and Statistical Analyses. D. Beniken, A. S. Ritleng, M. Azar, P. Honoré, S. Breau, A. Joulie, M. Mole, C. Bolliot, F. Chouraqui, F. Touam, F. André, N. Ouabdesselam, C. Partouche, G. Alexandre, A. Ganon, A. Champetier, H. Hue, D. Brosseau, C. Brochier, V. Thoirain, M. Rannou, D. Bornarel, S. Gillet, J. Delaune, E. Pambrun, L. Dequae-Merchadou, A. Frosch, G. Maradan, O. Cheminat, F. Marcellin, M. Mora, C. Protopopescu, P. Roux, C. Lions, M.-A. Loko, M. Winnock.