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MAJOR ARTICLE

Atherosclerotic Cardiovascular Events in Patients Infected With Human Immunodeficiency Virus and Hepatitis C Virus

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Background. An increased risk of cardiovascular disease (CVD) was reported in patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), without identifying factors associated with atherosclerotic CVD (ASCVD) events.

Methods. HIV-HCV coinfected patients were enrolled in the Agence Nationale de Recherches sur le Sida et les hépatites virales (ANRS) CO13 HEPAVIH nationwide cohort. Primary outcome was total ASCVD events. Secondary outcomes were coronary and/or cerebral ASCVD events, and peripheral artery disease (PAD) ASCVD events. Incidences were estimated using the Aalen-Johansen method. Factors associated with ASCVD were identified using cause-specific Cox proportional hazards models.

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A complete list of the Agence Nationale de Recherches sur le Sida et les hépatites virales CO13 HEPAVIH Study investigators is provided in the Supplementary Material.

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Results. At baseline, median age of the study population (N = 1213) was 45.4 (interquartile range [IQR] 42.1–49.0) years and 70.3% were men. After a median follow-up of 5.1 (IQR 3.9–7.0) years, the incidence was 6.98 (95% confidence interval [CI], 5.19–9.38) per 1000 person-years for total ASCVD events, 4.01 (2.78–6.00) for coronary and/or cerebral events, and 3.17 (2.05–4.92) for PAD ASCVD events. Aging (hazard ratio [HR] 1.06; 95% CI, 1.01–1.12), prior CVD (HR 8.48; 95% CI, 3.14–22.91), high total cholesterol (HR 1.43; 95% CI, 1.11–1.83), high-density lipoprotein cholesterol (HR 0.22; 95% CI, 0.08–0.63), statin use (HR 3.31; 95% CI, 1.31–8.38), and high alcohol intake (HR 3.18; 95% CI, 1.35–7.52) were independently associated with total ASCVD events, whereas undetectable baseline viral load (HR 0.41, 95% CI, 0.18–0.96) was associated with coronary and/or cerebral events.

Conclusions. HIV-HCV coinfected patients experienced a high incidence of ASCVD events. Some traditional cardiovascular risk factors were the main determinants of ASCVD. Controlling cholesterol abnormalities and maintaining undetectable HIV RNA are essential to control cardiovascular risk.

Keywords. HIV; hepatitis C virus; coinfection; atherosclerosis; cardiovascular.

Early and widespread access to antiretroviral therapy has contributed to a decrease in fatal events related to AIDS, improving the lifespan of people living with human immunodeficiency virus (HIV) (PLWH) [1, 2]. This increase in longevity has contributed to the transformation of HIV infection into a chronic disease, at a cost of an excess of noncommunicable diseases [1] such as cardiovascular disease (CVD) [1–4], and leading to increased morbimortality in PLWH [2, 5]. The pathophysiology of HIV-related atherosclerosis in PLWH on antiretroviral therapy is multifactorial [2]. Many traditional CVD risk factors affect PLWH [1–4], including arterial proinflammatory retrovirus activity [6], immune activation [1], drug toxicity [7], and disturbed lipid metabolism [7]. Hepatitis C virus (HCV) coinfection affects 6.2% of PLWH [8], and increases the risk of liver-related events and death [9]. Chronic HCV infection also contributes to atherosclerosis [10–12], myocardial infarction [13], and other CVD events [9]. Several studies have thus highlighted an increased risk of CVD events with HIV-HCV coinfection [14–19], especially compared with HIV alone [3, 4, 17, 20]. This coinfection may act synergistically to induce endothelial dysfunction [21], vascular inflammation [22], and insulin resistance [9]. Meanwhile, the advent of direct-acting antivirals (DAA) in 2014 has revolutionized the care of patients with HCV [23], allowing the achievement of a sustained virologic response (SVR) for almost all treated patients [24]. Hence, HCV SVR could decrease CVD events in HCV monoinfected patients [25–27] and in HIV-HCV coinfected patients [18]. However, in HIV-HCV coinfected patients, factors related to the occurrence of atherosclerotic CVD (ASCVD) have not yet been fully identified. Consequently, we sought to describe the incidence of total ASCVD events (including coronary, cerebrovascular, and peripheral artery disease [PAD]) and identify predictors of such events in this population.

METHODS

Study Design and Participants

Agence Nationale de Recherches sur le Sida et les hépatites virales (ANRS) CO13 HEPAVIH is a prospective, multicenter, nationwide, observational cohort study in HIV-HCV coinfected subjects that was initiated in France in December 2005. In this analysis, we used the database from this study, censored in December 2016, to identify patients who were chronically infected by HCV at the time of inclusion and had undergone ≥1 year of follow-up. Participants were included from December 2005 and followed through November 2016.

Clinic visits were scheduled annually for noncirrhotic patients and every 6 months for cirrhotic patients. For patients receiving HCV treatment, standardized questionnaires were used to collect clinical and biological data at the initiation and end of treatment and 6 months after the end of treatment.

The study complied with the Declaration of Helsinki and was approved by the institutional review board: Comité Ile de France 3, file no. 2234, ref CG/LG/CC 2005-255. Participants provided written consent to participate.

Follow-Up and Endpoint Definitions

Baseline was defined as the date of inclusion in the cohort. All CVD events that occurred during follow-up were recorded, based on information obtained from the medical files of patients from each center. Events experienced before inclusion were considered as prior CVD events. All CVD events were clinically adjudicated, independently validated, and classified as either coronary and/or cerebral ASCVD or PAD ASCVD by 2 cardiologists and 1 infectious diseases physician using American College of Cardiology/American Heart Association standard definitions [28, 29]. Study follow-up ended at the time of occurrence of a CVD event, the patient's death from a noncardiovascular cause, or their last clinic visit in the cohort.

The primary outcome was total ASCVD events, defined as the composite of:

1. Coronary and/or cerebral ASCVD events: any death from CVD related to myocardial infarction or sudden cardiac death with proven coronary artery disease; any acute coronary syndrome (with or without ST-segment elevation myocardial infarction or unstable angina pectoris requiring hospitalization); any coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft); or any ischemic stroke (transient or complete); and/or

2. PAD ASCVD events presumed to be of atherosclerotic origin: symptomatic PAD with or without transluminal arterial angioplasty, arterial bypass graft, or thrombectomy; and subclinical carotid artery stenosis documented by ultrasound (defined as ≥50% lumen stenosis) and aortic atherosclerotic disease (defined as an abdominal aortic aneurysm). Descending thoracic aneurysm and renal or mesenteric artery disease were excluded.

Secondary outcomes were the components of the primary outcome, taken separately. Other adjudicated CVD events were episodes of heart failure requiring hospitalization and venous thromboembolic disease requiring hospitalization.

Demographic characteristics included: age, sex, and body mass index (overweight was defined as body mass index >25 kg/m^2). Sociobehavioral variables and cardiovascular risk factors were tobacco consumption, illicit intravenous drug use, HCV transmission route (intravenous drug use, sexual, accidental exposure to blood, blood transfusion, or other), high alcohol intake (>14 glasses of alcohol per week for women and >21 glasses of alcohol per week for men), and psychiatric disorders (major depression, suicidality, [hypo]maniac episodes, posttraumatic stress, psychosis, generalized anxiety, alcohol or drug misuse/dependence, and any psychotropic treatment). Clinical variables included traditional CVD risk factors: arterial hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or hypertension treatment); total, high-density lipoprotein (HDL), and low-density lipoprotein cholesterol; diabetes mellitus (defined as a diabetes diagnosis, diabetes medications, or fasting blood glucose >126 mg/dL [7 mmol/L]); prior CVD; previous and current antiviral treatment for HCV and HIV; and renal failure [glomerular filtration rate <60 mL/min]. Metabolic data included lipid and blood glucose levels. Immunologic data included lymphocytic immunophenotyping for cluster of differentiation 4 (CD4), cluster of differentiation 8 (CD8), CD4:CD8 ratio, and cryoglobulinemia. Viral characteristics were HCV and HIV RNA at inclusion and HCV SVR (defined as an undetectable HCV viral load ≥24 weeks after the end of therapy with pegylated interferon or protease inhibitors and 12 weeks after the end of DAA treatment). SVR was considered as a time-dependent variable. Undetectable baseline HIV RNA was defined as HIV RNA below the detectability threshold of the device used. Liver characteristics were fibrosis stage (defined as a Fibrosis-4 score <1.45, absence of fibrosis, or moderate fibrosis; 1.45–3.25, mild fibrosis; >3.25, advanced fibrosis or cirrhosis) and liver stiffness (assessed by Fibroscan). With the exception of SVR, all variables were measured at baseline only.

Statistical Methods

Variables are reported as number and percentage or median and interquartile range (IQR), as appropriate. Incidence rates (and 95% confidence intervals [CI]) of total ASCVD, coronary and/or cerebral ASCVD, PAD ASCVD, and other CVD events were estimated per 1000 person-years (exact binomial distribution). Cumulative incidence rates of these events were estimated using the Aalen-Johansen method, accounting for competitive risks of death from another cause. The Aalen-Johansen estimator is a matrix version of the Kaplan-Meier estimator that can be used to estimate event probabilities over time in the presence of competing risk events [30].

Univariable and multivariable cause-specific Cox proportional hazard models were used, accounting for competing risks of death from another cause, to identify predictors of total ASCVD, coronary and/or cerebral ASCVD, and PAD ASCVD events. Univariable cause-specific Cox proportional hazards models were established for the demographic, sociobehavioral, clinical, biological, biochemical, metabolic, immunologic, virologic, and liver factors in patients without missing data for all variables in the analysis. All factors associated with the risk of total ASCVD events with a $P < .30$ in univariable analysis were included in a full multivariable model, in addition to variables included in the calculation of the Framingham score (sex, age, active smoking, diabetes, and arterial hypertension, considered as a binary variable, total cholesterol and HDL-cholesterol), HIV-related factors (baseline HIV RNA, CD4 count), and HCV-related factors (SVR and fibrosis stage). From this full multivariable model, a backward selection procedure was applied in patients with available data for all variables included in the full multivariable model. Factors associated with the risk of total ASCVD events with $P < .05$ and variables used for calculation of the Framingham score, HIV-related factors, and HCV-related factors were retained in the final model. Association measures and their 95% CIs between variables selected in the final model and total ASCVD events were estimated in the patients without missing data for the selected and forced variables. We checked whether the results remained consistent when the total and HDL-cholesterol variables, initially forced into the final model, were replaced, first by low-density lipoprotein cholesterol alone, and then by triglycerides and total cholesterol. The same strategy was used to identify factors associated with coronary and/or cerebral ASCVD events and PAD ASCVD events.

Statistical analyses were carried out using SAS version 9.4 (SAS Inc., Chicago, IL).

RESULTS

Baseline Characteristics

The study population comprised 1213 patients (Figure 1). Baseline characteristics are reported in Table 1. Median age was 45.4 (IQR 42.1–49.0) years and 70.3% were men. The prevalence of current smoking was 70.2%, cirrhosis 18.9%, diabetes 5.9%, and prior CVD 2.7%; 4.1% were on statins. Most of the patients (68.8%) were on HIV antiretroviral therapy.

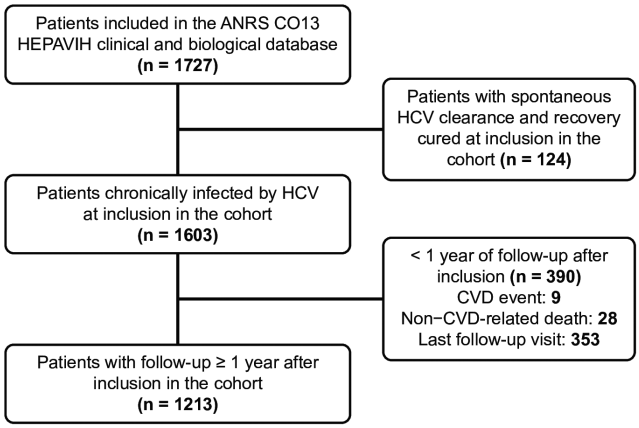

Figure 1. Flow chart of the HCV-HIV coinfected patients. Abbreviations: ANRS, Agence Nationale de Recherches sur le Sida et les hépatites virales; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Cardiovascular Disease Events

After a median follow-up of 5.1 (IQR 3.9–7.0) years, 54 CVD events were recorded in 52 patients, of which 84.6% were ASCVD events (46 events in 44 patients). Cumulative incidence rates after inclusion are shown in Figure 2. Median time to first ASCVD event was 3.4 (IQR 1.9–4.9) years. A total of 26 coronary and/or cerebral ASCVD events (including 5 ischemic strokes) and 20 PAD ASCVD events occurred (Table 2). Two patients had both coronary and/or cerebral ASCVD and PAD ASCVD events. PAD ASCVD events involved carotid and limb territories in 1 patient (who was asymptomatic) and symptomatic claudication or critical ischemia in 17 patients; 2 asymptomatic abdominal aortic aneurysms were reported (Table 2). Eight subjects with symptomatic lower limb artery disease events required vascular intervention (stent and/or vascular surgery). Two patients had critical limb ischemia. There were no cases of carotid endarterectomy.

The incidence of events was 6.98 (95% CI, 5.19–9.38) per 1000 person-years for total ASCVD events, 4.01 (95% CI, 2.78–6.00) per 1000 person-years for coronary and/or cerebral ASCVD (stroke 0.79 [95% CI, 0.33–1.89] per 1000 person-years), 3.17 (95% CI, 2.05–4.92) per 1000 person-years for PAD ASCVD events. Seven patients experienced a venous thromboembolic event and 1 had heart failure requiring hospitalization, resulting in incidences of 1.10 (95% CI, 0.53–2.32) and 0.16 (95% CI, 0.02–1.12) per 1000 person-years, respectively.

Factors Associated With ASCVD Events

The results of the multivariable analysis are provided in (Table 3). The following factors were significantly associated with a higher risk of total ASCVD: aging ($P = .03$), higher baseline total cholesterol ($P = .006$), prior CVD ($P < .001$), baseline statin use ($P = .001$), and high alcohol intake ($P = .008$). Higher baseline HDL-cholesterol ($P = .005$) was associated with a lower risk (Table 3).

Table 1. Baseline Characteristics of HIV-HCV Coinfected Patients at Inclusion in the ANRS CO13 HEPAVIH Cohort

	Total Cohort (N = 1213)
Demographic and lifestyle factors	
Age, y, median (IQR)	45.4 (42.1–49.0)
Male sex, no. (%)	853 (70.3)
Body mass index >25.0 kg/m^2 (n = 1182), no. (%)	230 (19.5)
Personal history of cardiovascular disease, no. (%)	33 (2.7)
Current tobacco consumption (n = 1198), no. (%)	841 (70.2)
Diabetes mellitus,[a] no. (%)	71 (5.9)
Arterial hypertension,[b] no. (%)	251 (20.7)
High alcohol intake,[c] (n = 1189), no. (%)	93 (7.8)
Illicit intravenous drug abuse, (n = 1199), no. (%)	66 (5.5)
Psychiatric disorders, no. (%)	218 (18.0)
Statin use, no. (%)	50 (4.1)
Laboratory values	
Total cholesterol, mg/dL (n = 1181), median (IQR)	154 (104–189)
HDL cholesterol, mg/dL (n = 1146), median (IQR)	39 (27–54)
LDL cholesterol, mg/dL (n = 1110), median (IQR)	81 (50–112)
Triglycerides, mg/dL (n = 1184), median (IQR)	115 (89–168)
Fasting blood glucose, mg/dL (n = 1168), median (IQR)	90 (83–99)
Glomerular filtration rate <60 mL/min (n = 1184), no. (%)	40 (3.4)
HCV and liver characteristics	
HCV contamination mode (n = 1011), no. (%)	
Intravenous drug use	674 (66.7)
Sexual	100 (9.9)
Blood exposure accident	13 (1.3)
Blood transfusion	63 (6.2)
Other	161 (15.9)
HCV treatment, no. (%)	
No antiviral treatment	602 (49.6)
Interferon	575 (47.4)
Protease inhibitor	50 (4.1)
Direct-acting antiviral	38 (3.1)
Liver stiffness value, kPa (n = 739), median (IQR)	7.1 (5.6–10.3)
FIB-4 score (n = 1195), median (IQR)	1.6 (1.1–2.6)
Cirrhosis,[d] (n = 739), No. (%)	140 (18.9)
Cryoglobulinemia (n = 938), no. (%)	396 (42.2)
HIV and immune characteristics	
HIV blood RNA undetectable (n = 1210), no. (%)	864 (71.4)
Current anti-retroviral therapy, no. (%)	835 (68.8)
CD4 lymphocytes count, /µL (n = 1205), median (IQR)	450 (313–650)
CD4:CD8 ratio (n = 1205), median (IQR)	0.6 (0.4–0.9)
Nadir CD4 lymphocytes, /µL (n = 1120), median (IQR)	150 (66–244)

SI conversion factor: to convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; blood glucose to millimoles per liter, multiply by 0.0555.

[a]Defined by a diabetes diagnosis or antidiabetic drug use or fasting blood glucose >126 mg/dL.

[b]Defined by systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or antihypertensive treatment use.

[c]Defined by alcohol intake >14 glasses of alcohol per week for women and >21 glasses of alcohol per week for men.

[d]Defined as liver stiffness >12.5 kPa.

Abbreviations: ANRS, Agence Nationale de Recherches sur le Sida et les hépatites virales; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; FIB-4, Fibrosis-4; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IQR, interquartile range; LDL, low-density lipoprotein.

Factors predictive of coronary and/or cerebral ASCVD events were higher baseline total cholesterol ($P < .001$) and prior CVD ($P < .001$). Higher baseline HDL-cholesterol ($P < .001$) and

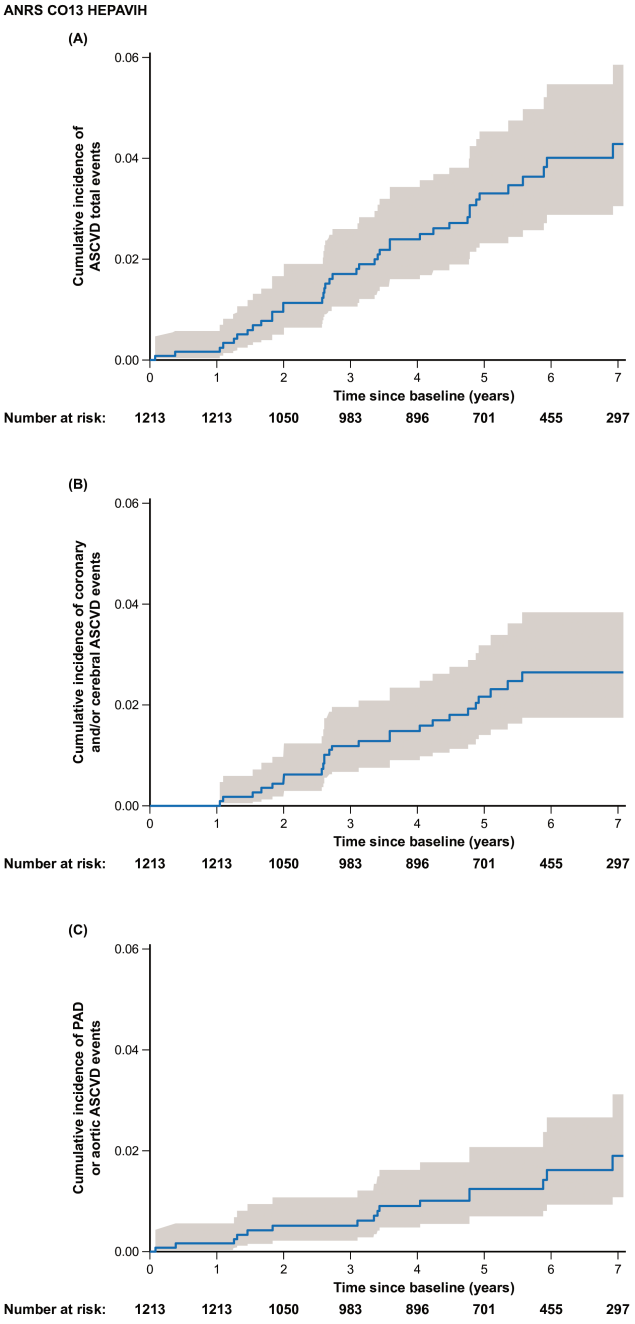

Figure 2. Cumulative incidence of cardiovascular events in HIV-HCV coinfected patients using the Aalen Johanson estimator: (A) total ASCVD events; (B) coronary and/or cerebral ASCVD events; and (C) peripheral artery disease events. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PAD, peripheral artery disease.

undetectable baseline HIV RNA ($P = .04$) were significantly associated with a lower risk of coronary and/or cerebral ASCVD (Table 3). This result remained when the covariables that were initially forced into the model were changed.

In multivariable analysis, which included components of the Framingham score and HCV characteristics, risk of PAD ASCVD was significantly associated with prior CVD ($P < .001$), high alcohol intake ($P = .02$), and baseline statin use ($P = .01$).

Table 2. ASCVD Events (N = 46) That Occurred in 44 HIV-HCV Coinfected Patients in the ANRS CO13 HEPAVIH Cohort

Events, No.	ASCVD events = 46
Major ASCVD events	26/46
Fatal myocardial infarction	2/26
Sudden cardiac death	2/26
STEMI	10/26
NSTEMI	1/26
Unstable angina requiring hospitalization	2/26
Percutaneous coronary intervention	3/26
Coronary arterial bypass grafting	1/26
Ischemic stroke	5/26
Peripheral arterial disease events	20/46
Symptomatic lower limb artery disease	17/20
Carotid stenosis >50%	1/20
Abdominal aortic aneurysms	2/20

Abbreviations: ANRS, Agence Nationale de Recherches sur le Sida et les hépatites virales; ASCVD, atherosclerotic cardiovascular disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; STEMI, acute coronary syndrome with ST elevation myocardial infarction.

Anti-HCV Drugs

At their last clinic visit during their follow-up, 459/1213 (37.8%) patients displayed HCV SVR, 388/1213 (32.0%) experienced HCV treatment failure, and 366/1213 (30.2%) had never received HCV treatment. Overall, 219/1213 (18.1%) of patients had received DAA. Fibrosis stage, HCV SVR, and CD4 lymphocyte count were not associated with any type of ASCVD events.

DISCUSSION

In this large, nationwide, prospective cohort of HIV-HCV coinfected patients in the ANRS CO13 HEPAVIH cohort, we observed a high incidence of ASCVD events, with similar incidences of coronary artery disease and PAD ASCVD events. Multivariable analyses demonstrated that some traditional risk factors (lipids and prior CVD) were predictive of total ASCVD events. Undetectable baseline HIV RNA was predictive of a lower risk of coronary and/or cerebral ASCVD events.

The high incidence of total ASCVD events observed in our cohort (6.98 per 1000 person-years) is in line with a previous study [7]. Other studies focused on either all or specific CVD events in PLWH [3, 4, 14–18]. Some of these studies showed that chronic HCV infection could promote CVD in PLWH without focusing on atherosclerosis [4, 14, 17, 18]. In the international Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) cohort of PLWH, in which 19% were coinfected by HCV, the incidence of ASCVD was 5.34 per 1000 person-years (from January 2009 to February 2016), based on a composite outcome that included myocardial infarction, sudden cardiac death, stroke, and invasive cardiovascular procedures (coronary bypass, coronary angioplasty, and carotid endarterectomy) [7].

Table 3. Factors Independently Associated With ASCVD Events Among HIV-HCV Coinfected Patients in the ANRS CO13 HEPAVIH Cohort

	Total ASCVD (n = 1095)		Coronary and/or Cerebral ASCVD (n = 1109)		PAD or Aortic ASCVD (n = 1095)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Male	2.32 (.79–6.78)	.12	2.67 (.60–11.85)	.20	2.63 (.56–12.30)	.22
Age (per 1-y increase)	1.06 (1.01–1.12)	.03	1.02 (.95–1.10)	.58	1.08 (1.00–1.18)	.07
Current tobacco consumption	2.11 (.91–4.88)	.08	1.93 (.63–5.91)	.25	1.64 (.54–5.03)	.39
Diabetes mellitus[a]	1.64 (.57–4.72)	.36	0.64 (.08–5.08)	.67	3.21 (.88–11.74)	.08
Arterial hypertension[b]	0.88 (.40–1.92)	.75	0.88 (.32–2.47)	.81	0.73 (.23–2.36)	.60
Total cholesterol (per 39 mg/dL increase)	1.43 (1.11–1.83)	.006	1.63 (1.24–2.15)	<.001	1.05 (.69–1.61)	.81
HDL cholesterol (per 39 mg/dL increase)	0.22 (.08–.063)	.005	0.08 (.02–0.34)	<.001	1.03 (.28–3.77)	.96
Prior cardiovascular disease event	8.48 (3.14–22.91)	<.001	13.94 (4.25–45.66)	<.001	10.90 (2.82–42.12)	<.001
High alcohol intake[c]	3.18 (1.35–7.52)	.008	–	–	4.17 (1.25–13.87)	.02
Statin use	3.31 (1.31–8.38)	.001	–	–	4.66 (1.40–15.59)	.01
HCV status		.24		.77		.84
No antiviral treatment	Ref		Ref		Ref	
Failure of antiviral treatment	0.71 (.32–1.57)		0.84 (.31–2.23)		0.62 (.16–2.38)	
HCV sustained virologic response	0.61 (.27–1.38)		0.91 (.29–2.82)		1.28 (.37–4.35)	
Liver fibrosis stage at baseline		.48		.65		.95
<1.45	Ref		Ref		Ref	
1.45–3.25	0.69 (.34–1.41)		0.68 (.26–1.75)		1.18 (.41–3.38)	
>3.25	0.60 (.22–1.66)		0.63 (.16–2.35)		1.15 (.28–4.68)	
Undetectable baseline HIV RNA	0.55 (.29–1.07)	.07	0.41 (.18–0.96)	.04	0.99 (.34–2.90)	.99
CD4 count[d]	1.03 (.92–1.15)	.66	1.06 (.92–1.23)	.43	1.01 (.85–1.20)	.9

Abbreviations: ANRS, Agence Nationale de Recherches sur le Sida et les hépatites virales; ASCVD, atherosclerotic cardiovascular disease; CD4, cluster of differentiation 4; CI, confidence interval; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HR, hazard ratio; Ref, reference.

[a]Diabetes diagnosis, diabetes medication, or fasting blood glucose >126 mg/dL.

[b]Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or hypertension treatment.

[c]Alcohol intake >14 glasses of alcohol per week for women and >21 per week for men. One glass contains 10 g of pure alcohol.

[d]Per 100/μL increase.

Compared with the D:A:D composite outcome, our definition of total ASCVD events also included PAD ASCVD events. Our PAD events predominantly included symptomatic lower limb artery disease (17 of 20, 85%).

How HCV could confer an increased risk of lower limb artery disease is unclear [10]. Epidemiologically, HCV appeared to be a specific risk factor associated with PAD in a recent study in PLWH [20], but the pathophysiology of HCV-related vasculopathy remains an issue. Few data are available regarding the descriptions of PAD in PLWH [20, 31] or with HIV-HCV coinfection [18]. Our incidence of PAD (3.17 per 1000 person-years) is lower than in the North American Veterans Aging Cohort Study (VACS) (11.9 per 1000 person-years) [20], but higher than in the Spanish nationwide HIV-HCV cohort Grupo de Estudio de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (GESIDA; 1.1 per 1000 person-years) [18]. This may be because only administrative data were used to identify PAD in the VACS cohort [20], whereas inpatient and outpatient medical files were used to confirm PAD in our study and in the GESIDA cohort [18]. In addition, there were different proportions of smokers, patients with diabetes, and illicit drug users (70.2%, 5.9%, and 5.5%, respectively, in our study vs 70.3%, 7.5%, and 18% in the VACS cohort [4, 14, 20], and 2.3% for diabetes and 80.4% for illicit drug use in GESIDA [18]). Again, nadir CD4 cell count could have also influenced the incidence of PAD, which was 119 cells/μL in VACS [20], 150 cells/μL in ANRS CO13 HEPAVIH [24], and 203 cells/μL in GESIDA [18]. Intravenous drug or cocaine use and cryoglobulinemia did not appear to be associated with PAD, even though they have been previously described [32, 33].

Surprisingly, our incidence of stroke (0.79 per 1000 person-years) was lower than in D:A:D [7] or VACS [4] (1.8 and 2.2 per 1000 person-years, respectively). This could be explained by a worse cardiovascular risk profile in VACS [4] and GESIDA [18] (with double the prevalence of hypertension and diabetes) compared with patients in the present study. Moreover, we defined ischemic stroke—as part of our composite outcome of total and coronary and/or cerebral ASCVD events—whereas other cohorts included ischemic and nonischemic strokes and some liver-related encephalopathies [15, 17, 20].

Predictors of ASCVD in our study were similar to those in previous studies [4, 14, 15, 21], underlining the role of traditional CVD risk factors (aging, total cholesterol, and prior CVD events) in HIV and HIV-HCV coinfected populations. As in previous studies [34–36], we found that undetectable baseline HIV RNA was associated with a reduced risk of coronary and/or cerebral ASCVD events. We did not find any association between HCV-related factors and risk of ASCVD events, particularly between DAA treatment and ASCVD events. However, HCV SVR has been associated with a reduction in CVD events in HCV-monoinfected patients in previous studies that also included nonatherosclerotic CVD events [9, 18, 25, 27]. Of note, the definition of CVD events in these studies was broader, including heart failure [9, 26, 27], arrhythmia [9], and cardiac valvulopathy [9], only in cirrhotic patients [9, 26]. In addition, the proportions of patients reaching SVR and treated by DAA were low in our study, which could limit statistical power to identify an association between SVR and ASCVD.

This study was not designed to identify causal associations, rather it aimed to identify independent predictors of ASCVD events. Statin use was identified as a predictor of ASCVD events in multivariable analysis; this may reflect indication bias, as statins might have been prescribed because of the presence of traditional cardiovascular risk factors. Our relatively low rate of statin use (4.1%) is in line with other international, multicenter cohorts [37, 38], indicating underuse of statins in primary and secondary prevention. However, statin use has been associated with improved virologic response rates to HCV treatment [39]. No data on antiplatelet drugs were available, which may account for the high incidence of PAD ASCVD events, including lower limb artery disease. Moreover, given the absence of a control group, the implication of HCV infection in the development of PAD ASCVD events is purely speculative. Current smoking was not associated with ASCVD events in our multivariable analyses, whereas high alcohol intake was, especially for PAD ASCVD events. A confusion bias may explain this result by simultaneous addiction and the high proportion of current smokers (70.2%) compared with those who have never smoked (20%) [9, 25]. The number of patients on DAA medications may not have been sufficient to determine an effect of HCV SVR in reducing the incidence of ASCVD at the end of the inclusion period in 2016. Consequently, follow-up after SVR may have been too short to observe a reduction in the incidence of ASCVD, as previously [40]. The present cohort is young (median age 45.4 years), which may explain the over representation of STEMI versus NSTEMI, which is usually predominant in older subjects. However, we could not exclude the possibility that NSTEMI related to type II myocardial infarction (nonobstructive coronary artery disease with troponin elevation was not included in the present study) or patients who were not hospitalized could have been missed. Finally, the relatively small number of ASCVD events could have resulted in unidentified predictive factors because of low statistical power.

CONCLUSIONS

This large, nationwide, prospective multicenter cohort including HCV-HIV coinfected patients with a long follow-up, showed a high incidence of ASCVD events, especially acute coronary syndrome and PAD. Traditional CVD risk factors were predictive of coronary and/or cerebral ASCVD events, whereas undetectable baseline HIV RNA was protective. PAD ASCVD events, in particular lower limb artery disease, was predominant and requires active diagnosis and intensive management, while controlling modifiable traditional cardiovascular

risk factors. HCV-related factors did not appear to be associated with the risk of cardiovascular events. The effect of HCV and DAA on ASCVD events remains to be elucidated.

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

Author contributions. L. W. and M. C. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: B. K. T., M. C., D. S.-C., C. Gilbert, P. S., L. W., F. B. Data acquisition: B. K. T., D. S.-C., A. C., L. E., M. A. L., C. K., I. P.-M., D. N., J. C., P. M., E. R., K. L., A. N., K. B., O. B., A. G., C. L.-C., D. G., L. A., C. Goujard., P. M., H. A., C. D., A. S., J.-L. L.-Z., D. Z., F. R., E. L., D. R., L. P., F. B., C. Gilbert, F. B.-S., F. D., P. S., L. W., F. B. Data analysis: B. K. T., M. C., D. S.-C., A. C., C. Gilbert, L. W., F. B. Data interpretation: B. K. T., M. C., D. S.-C., P. S., L.W., F. B. Drafting of the manuscript: B.K.T., M.C., L.W., D. S.-C., F.B. Critical revision of the article: B. K. T., M. C., D. S.-C., A. C., L. E., M. A. L., C. K., I. P.-M., D.N., J. C., P. M., E. R., K. L., A. N., K. B., O. B., A. G., C. L.-C., D. G., L. A., C. Goujard, P. M., H. A., C. D., A. S., J.-L. L.-Z, D. Z., F. R., E. L., D. R., L. P., F. B., C. Gilbert, F.B.-S., F.D., P.S., L.W., F.B. Final approval of the submitted version: B. K. T., M. C., D. S.-C., A. C., L. E., M. A. L., C. K., I. P.-M., D. N., J. C., P. M., E.R., K. L., A. N., K. B., O. B., A. G., C. L.-C., D. G., L. A., C. Goujard, P. M., H. A., C. D., A. S., J.-L. L.-Z., D. Z., F. R., E. L., D. R., L. P., F. B., C. Gilbert, F. B.-S., F. D., P. S., L. W., F. B.

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References

1. Shah ASV, Stelzle D, Lee KK, et al. Global burden of atherosclerotic cardiovascular disease in people living with HIV: systematic review and meta-analysis. Circulation **2018**; 138:1100–12.
2. Boccara F, Lang S, Meuleman C, et al. HIV and coronary heart disease: time for a better understanding. J Am Coll Cardiol **2013**; 61:511–23.
3. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med **2013**; 173:614–22.
4. Sico JJ, Chang C-CH, So-Armah K, et al. HIV status and the risk of ischemic stroke among men. Neurology **2015**; 84:1933–40.
5. Smith C, Sabin CA, Lundgren JD, et al; Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study Group. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. AIDS **2010**; 24:1537–48.
6. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. JAMA **2012**; 308:379–86.
7. Ryom L, Lundgren JD, El-Sadr W, et al; D:A:D study group. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. Lancet HIV **2018**; 5:e291–300.
8. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis **2016**; 16:797–808.
9. Nahon P, Bourcier V, Layese R, et al. Eradication of Hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. Gastroenterology **2017**; 152:142–56.e2.
10. Hsu YH, Muo CH, Liu CY, et al. Hepatitis C virus infection increases the risk of developing peripheral arterial disease: a 9-year population-based cohort study. J Hepatol **2015**; 62:519–25.
11. Petta S, Adinolfi LE, Fracanzani AL, et al. Hepatitis C virus eradication by direct-acting antiviral agents improves carotid atherosclerosis in patients with severe liver fibrosis. J Hepatol **2018**; 69:18–24.
12. Chew KW, Bhattacharya D, Horwich TB, et al. Performance of the pooled cohort atherosclerotic cardiovascular disease risk score in hepatitis C virus-infected persons. J Viral Hepat **2017**; 24:814–22.
13. Butt AA, Yan P, Chew KW, et al. Risk of acute myocardial infarction among hepatitis C virus (HCV)-positive and HCV-negative men at various lipid levels: results from ERCHIVES. Clin Infect Dis **2017**; 65:557–65.
14. Freiberg MS, Cheng DM, Kraemer KL, Saitz R, Kuller LH, Samet JH. The association between hepatitis C infection and prevalent cardiovascular disease among HIV-infected individuals. AIDS **2007**; 21:193–7.
15. Bedimo R, Westfall AO, Mugavero M, Drechsler H, Khanna N, Saag M. Hepatitis C virus coinfection and the risk of cardiovascular disease among HIV-infected patients. HIV Med **2010**; 11:462–8.
16. Sosner P, Wangermez M, Chagneau-Derrode C, Le Moal G, Silvain C. Atherosclerosis risk in HIV-infected patients: the influence of hepatitis C virus co-infection. Atherosclerosis **2012**; 222:274–7.
17. Fernández-Montero JV, Barreiro P, de Mendoza C, Labarga P, Soriano V. Hepatitis C virus coinfection independently increases the risk of cardiovascular disease in HIV-positive patients. J Viral Hepat **2016**; 23:47–52.
18. Berenguer J, Rodríguez-Castellano E, Carrero A, et al. Eradication of hepatitis C virus and non-liver-related non-acquired immune deficiency syndrome-related events in human immunodeficiency virus/hepatitis C virus coinfection. Hepatology **2017**; 66:344–56.
19. Freiberg MS, Chang CC, Skanderson M, et al; Veterans Aging Cohort Study. The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. Circ Cardiovasc Qual Outcomes **2011**; 4:425–32.
20. Beckman JA, Duncan MS, Alcorn CW, et al. Association of human immunodeficiency virus infection and risk of peripheral artery disease. Circulation **2018**; 138:255–65.
21. de Castro IF, Micheloud D, Berenguer J, et al. Hepatitis C virus infection is associated with endothelial dysfunction in HIV/hepatitis C virus coinfected patients. AIDS **2010**; 24:2059–67.
22. Shaked I, Hanna DB, Gleißner C, et al. Macrophage inflammatory markers are associated with subclinical carotid artery disease in women with human immunodeficiency virus or hepatitis C virus infection. Arterioscler Thromb Vasc Biol **2014**; 34:1085–92.
23. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al; AI444040 Study Group. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med **2014**; 370:211–21.
24. Sogni P, Gilbert C, Lacombe K, et al. All-oral direct-acting antiviral regimens in HIV/hepatitis C virus-coinfected patients with cirrhosis are efficient and safe: real-life results from the prospective ANRS CO13-HEPAVIH cohort. Clin Infect Dis **2016**; 63:763–70.
25. Lee KK, Stelzle D, Bing R, et al. Global burden of atherosclerotic cardiovascular disease in people with hepatitis C virus infection: a systematic review, meta-analysis, and modelling study. Lancet Gastroenterol Hepatol **2019**; 4:794–804.
26. Cacoub P, Nahon P, Layese R, et al; ANRS CO12 CirVir group. Prognostic value of viral eradication for major adverse cardiovascular events in hepatitis C cirrhotic patients. Am Heart J **2018**; 198:4–17.
27. Butt AA, Yan P, Shuaib A, Abou-Samra A-B, Shaikh OS, Freiberg MS. Direct-acting antiviral therapy for HCV infection is associated with a reduced risk of cardiovascular disease events. Gastroenterology **2019**; 156:987–96.e8.
28. Hicks KA, Tcheng JE, Bozkurt B, et al; American College of Cardiology; American Heart Association. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards

(Writing Committee to Develop Cardiovascular Endpoints Data Standards). Circulation **2015**; 132:302–61.
29. Creager MA, Belkin M, Bluth EI, et al; Writing Committee to Develop Clinical Data Standards for Peripheral Atherosclerotic Vascular Disease. **2012** ACCF/AHA/ACR/SCAI/SIR/STS/SVM/SVN/SVS key data elements and definitions for peripheral atherosclerotic vascular disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Peripheral Atherosclerotic Vascular Disease). Circulation **2012**; 125:395–467.
30. Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. Scand J Stat **1978**; 5:141–50.
31. Knudsen AD, Gelpi M, Afzal S, et al. Brief report: prevalence of peripheral artery disease is higher in persons living with HIV compared with uninfected controls. J Acquir Immune Defic Syndr 1999 **2018**; 79:381–5.
32. Lucas GM, Atta MG, Fine DM, et al. HIV, cocaine use, and hepatitis C virus: a triad of nontraditional risk factors for subclinical cardiovascular disease. Arterioscler Thromb Vasc Biol **2016**; 36:2100–7.
33. Dakour-Aridi H, Arora M, Nejim B, Locham S, Malas MB. Association between drug use and in-hospital outcomes after infrainguinal bypass for peripheral arterial occlusive disease. Ann Vasc Surg **2019**; 58:122–33.e4.
34. Drozd DR, Kitahata MM, Althoff KN, et al. Increased risk of myocardial infarction in HIV-infected individuals in North America compared with the general population. J Acquir Immune Defic Syndr 1999 **2017**; 75:568–76.
35. Chow FC, Bacchetti P, Kim AS, Price RW, Hsue PY. Effect of CD4+ cell count and viral suppression on risk of ischemic stroke in HIV infection. AIDS **2014**; 28:2573–7.
36. El-Sadr WM, Lundgren JD, Neaton JD, et al; Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med **2006**; 355:2283–96.
37. Lang S, Lacombe JM, Mary-Krause M, et al; French Hospital Database on HIV. Is impact of statin therapy on all-cause mortality different in HIV-infected individuals compared to general population? Results from the FHDH-ANRS CO4 Cohort. PLoS One **2015**; 10:e0133358.
38. Clement ME, Park LP, Navar AM, et al. Statin utilization and recommendations among HIV- and HCV-infected veterans: a cohort study. Clin Infect Dis **2016**; 63:407–13.
39. Butt AA, Yan P, Bonilla H, et al; ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans) Study Team. Effect of addition of statins to antiviral therapy in hepatitis C virus-infected persons: results from ERCHIVES. Hepatology **2015**; 62:365–74.
40. Mocroft A, Lundgren J, Gerstoft J, et al. Clinical outcomes in persons coinfected with human immunodeficiency virus and Hepatitis C virus: impact of hepatitis C virus treatment. Clin Infect Dis **2020**; 70:2131–40.