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Impact of immunodepression and moderate alcohol consumption on coronary and other arterial disease events in an 11-year cohort of HIV-infected patients on antiretroviral therapy

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ABSTRACT

Objective: To investigate the relationship between response to antiretroviral therapy (ART), alcohol use and occurrence of a major coronary or other arterial disease event (CADE) in HIV-infected individuals.

Design: A cohort study. A Cox model was used to identify the correlates of a first occurrence of a major CADE.

Setting: The French ANRS CO8 APROCO-COPILOTE cohort was set up in 1997 to study clinical progression and patient-reported outcomes (PRO) after initiating a protease inhibitor-containing ART. Clinical data were retrieved from medical records. Self-administered questionnaires collected data on PRO and behaviours, including alcohol use.

Participants: Metabolic data were only available for a subgroup (n=675) of the study group (n=1154).

Main outcome measures: Major coronary or other arterial disease first event.

Results: Over the 11-year follow-up, 49 major CADE were observed, with an incidence rate (95% CI)=0.75 (0.57 to 0.99) per 100 person-years. Immunodepression (CD4 cell count <200 cells/mm^3) was associated with an increased risk of CADE (adjusted HR (95% CI)=2.52(1.15 to 5.48)) after adjustment for female gender (0.25(0.08 to 0.83)), age (1.07(1.04 to 1.10)) and smoking>20 cigarettes/day (4.19(2.17 to 8.11)). Moreover, individuals with moderate alcohol consumption (≤4(3) alcohol units (AU)/day for men (women)) had a lower risk of CADE (0.38(0.20 to 0.71)) than alcohol abstainers, although the risk for those drinking>4(3) AU/day for men(women) was not significantly different from this latter group. These associations remained valid after adjustment for metabolic disorders. No significant association with exposure to any specific antiretroviral was detected.

Conclusions: In the long term, absence of immunodepression and moderate alcohol consumption remain associated with a lower risk of a major CADE. Combined interventions to reduce CADE-risk-related behaviours including adherence counselling for assuring long-term immunological response to ART in HIV-infected individuals are now a clinical and public health priority.

ARTICLE SUMMARY

Article focus

- Major coronary or other arterial disease events (CADE) are frequent in HIV-infected individuals receiving antiretroviral therapy.
- Although some antiretroviral classes can increase the risk of CADE, it is still controversial to what extent immune reconstitution and other factors like moderate alcohol consumption can reduce the risk of CADE in this population.

Key messages

- Moderate alcohol consumption and absence of immunodepression can be beneficial to reduce the risk of CADE in HIV-infected patients.
- A reduced immunological response to the antiretroviral treatment over a long follow-up may have a more important impact on CADE than exposure to a specific antiretroviral drug.

Strengths and limitations of this study

- This paper suggests the importance of combined risk-reductional interventions including adherence counselling for assuring long-term immunological response and decrease the risk of CADE.

INTRODUCTION

Cardiovascular disease risk factors (including, for example, hypertension and tobacco

use), as well as immunological status[1] are major predictors of atherosclerosis in HIV-infected women and men. Although some antiretroviral (ARV) therapy drugs[2–5] have consistently been found to be associated with coronary arterial disease or myocardial infarction (MI) in these patients, more recently Butt *et al*[6] put into evidence the negative effect of HIV viral replication on heart failure. In one study, patients, having experienced a MI, presented a lower baseline and proximal CD4 cell counts than those who did not, while no association was found between cardiovascular disease events and specific ARV agents.[7] Moreover, known factors associated with cardiovascular risk[8] such as hyperlipidaemia and insulin resistance[9–11] are increasingly becoming a major clinical concern in ARV-treated individuals.

Although excessive alcohol use may be frequent in HIV-infected individuals, its impact on the occurrence of cardiovascular disease in this population has been less investigated. Excessive alcohol consumption also plays a major role in HIV risk-taking behaviours, particularly in men who have sex with men and drug users.[12 13] In HIV-infected individuals, excessive alcohol use is known to compromise patients' response to antiretroviral therapy (ART) through a reduced adherence[14–17] and to predict the HIV progression and increased mortality,[18–21] mostly from liver diseases.[22–25] Some recent cross-sectional analyses in HIV-infected and uninfected men have found that heavy alcohol consumption is associated with a higher risk of cardiovascular disease.[26 27] On the other hand, in uninfected adults, moderate alcohol consumption has been found to be associated with a reduced cardiovascular mortality,[28] improved lipid profiles, an increased insulin sensitivity and a reduced risk of MI.[29] However, this association has not yet been studied in longitudinal studies involving HIV-infected populations including women. Moreover, there are as yet no consistent results in the literature regarding the role that alcohol use plays in exacerbating cardiovascular risk in ARV-treated patients and to what extent it can confound or boost the effect of immunovirological response to ART, ART-associated dyslipidaemia and insulin resistance on the risk of cardiovascular disease events.

We used data from the 11-year follow-up of the APROCO-COPILOTE cohort of patients receiving ART since 1997 to investigate the relationship among viral load, CD4 cell count, alcohol consumption and the first occurrence of a major coronary or other arterial disease event (CADE), after adjustment for known risk factors including metabolic disorders.

METHODS

The French APROCO-COPILOTE cohort (ANRS CO8) was designed to study the clinical, immunological, virological and sociobehavioural course of HIV disease in HIV-1-positive individuals who began undergoing the first generation of potent ART (treatment regimens including protease inhibitors (PI)). The study was approved by the Ethics Committee of Cochin Hospital (Paris) and an informed consent was obtained from all participants.

Setting

Patients were enrolled in the cohort at their first PI-based ART prescription between May 1997 and June 1999 (n=1281) in 47 French centres, and clinically followed up every 4 months thereafter, up to the month 132 (M132).

Patients

In the present study were included all patients who underwent either two alcohol assessments or one alcohol assessment just preceding the CADE over the entire follow-up (n=1154).

Medical questionnaire

The medical questionnaire at enrolment (M0) collected retrospective data about patient's HIV history including HIV transmission category, time since HIV diagnosis, a previous exposure to ARV treatment before enrolment and a coinfection with hepatitis C virus (HCV) defined as having positive HCV RNA and/or positive HCV antibodies. This information was complemented by medical questionnaires, completed by the HIV physicians at each follow-up visit, which collected clinical and laboratory data (plasma HIV RNA level, CD4 cell count, HIV clinical stage, aspartate transaminase (AST) and alanine transaminase (ALT) levels), as well as data on the ARV regimen prescribed. A third form, based on updated medical records, detailed all clinical severe events, including cardiovascular events, occurring during the study period. Information on metabolic disorders was available at M12 for a subset of cohorts' patients, who participated in a parallel cross-sectional survey, designed to study clinical and laboratory metabolic complications.[30] These 'metabolical' data included height, weight, hypertriglyceridaemia, hypercholesterolaemia, personal history of coronary heart disease (CHD) and hypertension and finally any family history of CHD.

At each follow-up visit, CD4 cell count was measured by standardised flow cytometry, and plasma HIV RNA levels were measured using the assay routinely available in each participating centre. Immunodepression was defined by CD4 cell count <200 cells/mm^3; viral load was classified as detectable if it was greater than the threshold value specific to each centre where the assay was performed, and to each period. The detectability threshold of the viral load ranged from 20 to 500 copies/ml for the M0–M20 period and from 20 to 400 copies/ml for the rest of the follow-up. HIV clinical stage was defined using the 1993 Centres for Disease Control and Prevention (CDC) clinical classification system.[31]

Serum triglyceride and cholesterol levels were measured after a 12-hour overnight fast. Hypertriglyceridaemia was defined as a triglyceride level ≥2.2 mmol/l, while

hypercholesterolaemia was defined as a total cholesterol level ≥5.5 mmol/l.

Outcome

The details of all clinically severe events, including cardiovascular events, which occurred during the follow-up, were obtained from medical records and validated by the cohort's validation committee.[30] The classification of clinically severe events was based on the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (http://www.who.int/classifications/icd/en/).[1] An event was considered severe when it required a medical intervention, hospitalisation, when hospitalisation was extended owing to the event's occurrence, when it led to a life-threatening condition or when it resulted in death. A group of cardiologists specifically validated the events selected as outcomes for this study. Among cardiovascular events, only major CADE were selected for this analysis as follows (listed in a singular form): MI, stroke, CHD, peripheral arterial disease and cardiovascular surgery for coronary disease. We excluded the following from the definition of the outcome: heart failure, cardiac arrhythmia, phlebitis, pulmonary embolism and peripheral venous diseases to keep only severe or life-threatening cardiovascular events in the analysis.

Self-administered questionnaire

A self-administered questionnaire collected—at M0, M4, M12 and every 8 months thereafter during the first 5 years of the follow-up, then yearly thereafter—data on sociodemographic characteristics including age, gender and educational level. Among other psychosocial and behavioural information, it also collected details on depressive symptoms, tobacco use, alcohol consumption, self-reported ART-related symptoms and adherence to ART.

Depression was measured using the validated French version of the Centre for Epidemiologic Studies Depression Scale (CES-D), which is a 20-item scale commonly used in studies involving HIV-infected patients.[32]

Tobacco and alcohol consumption were evaluated during the previous 4 weeks. Alcohol consumption was assessed using two questions about the frequency of consumption and quantity consumed daily, if applicable.

A 13-item scale, comprising the French version of the symptom index validated by Justice *et al*[33] and described elsewhere,[34] collected information about self-reported symptoms. Five other questions were coined for gathering information about adherence to ART, according to the methodology established by the AIDS Clinical Trial Group.[35]

Statistical analysis

As the results of the analysis on the whole dataset (n=1154) could be affected by the lack of important predictors of CADE-like hypertriglyceridaemia or hypercholesterolaemia, we conducted a secondary analysis on a subset of patients who had additional metabolic disorders data. More specifically, two analyses on the following study populations were performed to study predictors of a major CADE:

1. First analysis: the study population included all patients who underwent either two alcohol assessments or one alcohol assessment just preceding the event over the entire follow-up (n=1154). The follow-up period was M0–M132.
2. Second analysis: the study population was restricted to the subset of patients with available data on metabolic disorders, measured at M12 (n=675). Consequently, only events occurring after M12 were considered in this second analysis.

The WHO body mass index (BMI) categories were used in the analysis: underweight and overweight/obese patients were defined, respectively, as having a BMI lower than 18.5 and greater than 25.

A time-varying cumulative measure of the time exposure to specific ARV medications (abacavir, efavirenz, nevirapine, lopinavir and PI) was computed during which ART included a specific drug from this list, from cohort enrolment to the date of each follow-up visit.

CD4 cell count was tested either as a continuous variable or recoded in categories. The dichotomous variable using the cutoff of 200 cells/mm^3 was found to be the most predictive of the outcome (using Cox models and bias-corrected Akaike's information criterion AICc).[36]

Tobacco consumption was dichotomised in two categories: more than 20 cigarettes/day versus other.[37] The average number of alcohol units (AU) consumed per day[38] was computed using the two questions on alcohol consumption and then recoded in four categories (abstainers; ≤1 AU/day; >1 and ≤4(3) AU/day for men (women); >4(3) AU/day for men(women)), to test a gradient effect. We used information on AST and ALT liver enzymes to test their correlation with alcohol consumption as a validation test of self-reported alcohol consumption. As normal liver enzymes' reference ranges for each laboratory were not available in our data set, we used a universal cutoff of ALT>50 units/l of serum as an indicator of liver injury, and the AST/ALT ratio (in conjunction with ALT>50 IU/l) as a marker of possible cirrhosis and/or alcoholic liver disease (for AST/ALT>1) and advanced alcoholic liver disease (for AST/ALT>2). We found a positive significant association between excessive alcohol consumption, and these two indicators of liver injury (after adjusting for HCV status, table 1), which would suggest good accuracy of the self-reported data on alcohol consumption.

Patients were classified as non-adherent if they reported taking less than 100% of prescribed medications during the previous 4 weeks, using a validated algorithm.[39] A patient with a CES-D score value above 17 (men) or 23 (women) was considered as presenting depressive symptoms.[40]

Incidence rate of a major CADE was computed as the number of cases divided by the number of person-years of the follow-up. The follow-up duration was calculated

Table 1 Association between alcohol consumption and liver injury indicators, after adjustment for HCV status, among HIV-infected patients receiving ART (ANRS CO8 APROCO-COPILOTE cohort—random effects logistic models, all patients—n=1154, follow-up period M0–M132)

	ALT>50 IU/l & AST/ALT>1		ALT>50 IU/l & AST/ALT>2	
	AOR (95%CI)	p-value	AOR (95%CI)	p-value
Alcohol consumption*				
abstainers (ref.)	1		1	
≤1 AU/day	0.7 (0.5–1.2)	0.228	2.8 (0.4–18.4)	0.292
>1 and ≤4(3) AU/day for men(women)	1.0 (0.6–1.8)	0.847	0.7 (0.0–10.1)	0.772
>4(3) AU/day for men(women)	4.9 (2.4–9.8)	$<10^{-3}$	29.0 (3.4–250)	0.002
HCV infection at M0	12.9 (7.6–21.8)	$<10^{-3}$	11.2 (2.7–46.4)	0.001

ALT, alanine transaminase; ART, antiretroviral therapy; AOR, adjusted OR from a random effects logistic model; AST, aspartate transaminase; AU, alcohol unit; HCV, hepatitis C virus.
*Time-varying variable (the last available value before each visit).

as the difference in days from the enrolment to the date of the CADE, death or last visit, whichever occurred first. Follow-up of patients experiencing a major CADE was censored after the date of the first CADE. We used a Cox proportional hazards model to identify characteristics associated with the first occurrence of a major CADE. Psychosocial characteristics—depressive symptoms, tobacco and alcohol consumption, self-reported symptoms, CD4 cell count and viral load—were evaluated at each visit and used as time-varying covariates in the statistical analysis. All the other covariates were used as fixed variables (measured at M0, M1 or M12). For time-varying factors, the last known value was carried forward in the case of missing data at a scheduled visit. In the case of an event occurring between two consecutive follow-up visits, the values for the time-varying variables measured at the visit preceding the event were used. Covariates with a p-value<0.25 in univariate Cox analyses were considered eligible for the multivariate Cox model. Three building strategies for the final model were compared: a backward stepwise selection procedure based on the Wald test ($p<0.05$), a selection procedure based on the second-order or bias-corrected Akaike's information criterion AICc,[36] and finally a selection procedure based on the Schwartz Bayesian information criterion BIC.[41] All three strategies selected the same final multivariate model. Interaction effects among the factors of the multivariate final model were tested. The proportional hazards assumption was verified globally for the multivariate models and separately with respect to each covariate, using both Kaplan-Meier estimates and tests based on Schoenfeld residuals.[42] A residual analysis for outliers' detection was performed, and the sensitivity of the model to influential outliers was tested.

Several sensitivity analyses were performed. First, we excluded all patients with a history of CHD and re-ran the model to verify whether the pattern of factors would remain unchanged.

Second, the patients who died due to alcoholic cirrhosis were excluded from the study. A third analysis was performed separately on the subgroups of patients coinfected with HCV and those not coinfected with HCV.

All analyses were performed using the Stata Intercooled software, V.12.1.

RESULTS

A total of 1154 patients were included in the present study, accounting for 9401 person-visits. When comparing the selected patients (n=1154) with those included in the cohort, but excluded from the study owing to missing alcohol data (n=127), no significant difference was found for gender, age at enrolment, ARV naivety, CDC clinical stage, baseline CD4 cell counts and HIV viral load at M0 (data not shown).

Median (IQR) duration of the follow-up of the selected patients, from their first visit after the ART prescription (M1) until M132, was 5.9 (1.8 to 9.4) years. The loss to follow-up of the cohort was 0.14% at M12, 0.31% at M36, 0.44% at M60 and 0.76% at M120.

Over the 11-year follow-up of the cohort, a total of 85 severe cardiovascular events were observed. These included 49 major CADE as follows: MI (n=30), CHD (n=4), stroke (n=7), peripheral arterial disease (n=7) and cardiovascular surgery for coronary disease (n=1). The distribution of the other 36 severe cardiovascular events was as follows: phlebitis/pulmonary embolism (n=22), cardiomyopathy/congestive heart failure (n=5), cardiac dysrhythmia (n=6), cerebral haemorrhage (n=2) and aortic aneurysm (n=1).

The incidence rate (95% CI) of all severe cardiovascular events was 1.3 (1.0 to 1.6) per 100 person-years, while for a major CADE the incidence rate was 0.75 (0.57 to 0.99) per 100 person-years. Of the 49 major CADE, 40 occurred after M12. Furthermore, the major CADE incidence over the period M12–M132 was 0.89 (0.66 to 1.22) per 100 person-years.

The distribution of factors associated with a major CADE, as well as the results of univariate and multivariate Cox models are reported in table 2 for the entire study population (n=1154). Table 3 focuses instead on the subset of patients with available data on metabolic disorders (n=675).

Women represented 22% of the study population (n=1154; table 2). The mean (SD) age at the baseline

Table 2 Factors associated with the first occurrence of a major CADE among HIV-infected patients receiving ART (ANRS CO8 APROCO-COPILOTE cohort—univariate and multivariate Cox proportional hazard models, all patients—n=1154, follow-up period M0–M132)

			Univariate analyses		Multivariate analysis	
	% of patients or mean (SD)	% of miss.data	HR (95% CI)	p-value	AHR (95% CI)	p-value
Socio-demographic and psychosocial characteristics						
Female gender	22.0	0	0.26 (0.08–0.84)	0.025	0.25 (0.08–0.83)	0.024
Age at M0*—*years*	37.7 (9.5)	0	1.06 (1.03–1.09)	$<10^{-3}$	1.07 (1.04–1.10)	$<10^{-3}$
Secondary-school certificate at M0*	31.3	7.3	0.51 (0.26–1.01)	0.054		
Alcohol consumption at M0*		0				
abstainers (ref)	18.8		1			
≤4(3) AU/day for men(women)	75.3		0.47 (0.24–0.89)	0.021		
>4(3) AU/day for men(women)	5.9		0.75 (0.21–2.63)	0.648		
Alcohol consumption†		0				
abstainers (ref)	18.6		1		1	
≤4(3) AU/day for men(women)	77.2		0.44 (0.24–0.81)	0.009	0.38 (0.20–0.71)	0.002
>4(3) AU/day for men(women)	4.1		1.04 (0.30–3.58)	0.953	0.46 (0.13–1.63)	0.229
Tobacco consumption >20 cig/day†	15.8	0.1	3.17 (1.73–5.83)	$<10^{-3}$	4.19 (2.17–8.11)	$<10^{-3}$
Depressive symptoms§†	32.0	1.8	1.22 (0.67–2.21)	0.512		
Number of self-reported symptoms (excluding lipodystrophy) †	4.8 (3.8)	0.1	1.01 (0.95–1.08)	0.694		
Number of self-reported lipodystrophy symptoms†	2.5 (2.6)	0.4	1.07 (0.96–1.18)	0.223		
ART adherence†	63.2	0.3	2.42 (1.17–5.02)	0.017		
Clinical characteristics						
HIV transmission category*		0				
Homosexual	40.6		0.99 (0.42–2.34)	0.988		
Injecting drug use	17.8		0.92 (0.50–1.70)	0.793		
Other (ref)	41.6		1			
CDC clinical stage A at M0*	51.2	0	0.44 (0.23–0.85)	0.014		
HCV infection at M0*	22.4	4.3	1.16 (0.59–2.29)	0.655		
Time since HIV diagnosis at M0—*years**	4.7 (4.2)	0.9	1.01 (0.94–1.08)	0.822		
Duration of exposure to efavirenz—*years*†‡	1.0 (2.2)	0	0.86 (0.71–1.03)	0.102		
Duration of exposure to nevirapine—*years*† ‡	0.9 (2.2)	0	0.91 (0.78–1.07)	0.279		
Duration of exposure to abacavir—*years*† ‡	1.0 (2.1)	0	0.98 (0.84–1.13)	0.748		
Duration of exposure to lopinavir—*years*† ‡	0.4 (1.5)	0	1.01 (0.85–1.20)	0.929		
Duration of exposure to PI-based regimen—*years*† ‡	3.2 (3.1)	0	1.03 (0.92–1.15)	0.615		
Antiretroviral naivety at M0*	44.4	0	1.14 (0.64–2.02)	0.654		
CD4 cell count <200 cells/mm^3 at M0*	35.9	0.1	0.99 (0.55–1.80)	0.978		
Detectable viral load at M0*	94.0	0.3	0.81 (0.25–2.61)	0.725		
CD4 cell count <200 cells/mm^3†	13.7	0.02	2.48 (1.15–5.33)	0.020	2.52 (1.15–5.48)	0.020
Detectable viral load†	43.4	0.7	0.99 (0.53–1.84)	0.980		

(A)HR, (adjusted) HR; ART,antiretroviral therapy; CADE, coronary or other arterial disease event; CHD, coronary heart disease.
*Fixed variable (measured at M0 or M1);
†Time-varying variable (the last available value before each visit); percentages and averages were computed on all follow-up visits for time-varying variables;
‡Percentages and averages are computed at the end of the follow-up (last available visit for each patient);
§Depressive symptoms: the Centre for Epidemiologic Studies Depression Scale score is >17 for men and >23 for women.

Table 3 Factors associated with the first occurrence of a major CADE among HIV-infected patients receiving ART (ANRS CO8 APROCO-COPILOTE cohort—univariate and multivariate Cox proportional hazard models, patients with available metabolic data—n=675, follow-up period M12–M132)

			Univariate analyses		Multivariate analysis	
	% of patients or mean (SD)	% of miss.data	HR (95% CI)	p-value	AHR (95% CI)	p-value
Socio-demographic and psychosocial characteristics						
Female gender	19.0	0	0.33 (0.08–1.40)	0.134		
Age at M0—*years**	38.4 (9.5)	0	1.04 (1.01–1.07)	0.013	1.05 (1.02–1.09)	0.003
Secondary-school certificate at M0*	35.4	6.7	0.34 (0.14–0.84)	0.019		
Alcohol consumption at M0*		0				
abstainers (ref)	15.1		1			
≤4(3) AU/day for men(women)	78.4		0.44 (0.18–1.03)	0.059		
>4(3) AU/day for men(women)	6.5		1.04 (0.26–4.05)	0.959		
Alcohol consumption†		0				
abstainers (ref)	16.5		1		1	
≤4(3) AU/day for men(women)	79.1		0.27 (0.13–0.58)	0.001	0.23 (0.11–0.49)	$<10^{-3}$
>4(3) AU /day for men(women)	4.4		1.19 (0.33–4.23)	0.792	0.55 (0.14–2.14)	0.390
Tobacco consumption >20 cig/day†	15.7	0.1	3.58 (1.70–7.54)	0.001	5.59 (2.43–12.8)	$<10^{-3}$
Depressive symptoms¶†	31.9	1.50	1.83 (0.90–3.73)	0.094		
Number of self-reported symptoms (excluding lipodystrophy)†	4.8 (3.8)	0.02	1.03 (0.95–1.12)	0.463		
Number of self-reported lipodystrophy symptoms†	2.6 (2.7)	0.16	1.10 (0.98–1.24)	0.111		
ARV adherence†	63.6	0.2	1.63 (0.70–3.81)	0.260		
Clinical characteristics						
HIV transmission category*		0				
Homosexual (ref)	44.0		1			
Injecting drug use	15.0		2.08 (0.75–5.73)	0.156		
Other	41.0		1.32 (0.59–2.93)	0.499		
CDC clinical stage A at M0*	50.8	0	0.43 (0.19–0.97)	0.041		
HCV infection at M0*	19.8	3.8	2.05 (0.94–4.47)	0.071		
Duration since HIV diagnosis at M0—*years**	4.7 (4.2)	1.2	1.04 (0.96–1.13)	0.311		
Duration of exposure to efavirenz—*years*† §	1.4 (2.5)	0	0.89 (0.73–1.08)	0.236		
Duration of exposure to nevirapine—*years*† §	1.0 (2.3)	0	0.83 (0.66–1.06)	0.147		
Duration of exposure to abacavir—*years*† §	1.2 (2.3)	0	0.99 (0.85–1.17)	0.971		
Duration of exposure to lopinavir—*years*† §	0.5 (1.5)	0	1.07 (0.88–1.30)	0.505		
Duration of exposure to PI-based regimen—*years*† §	3.9 (3.1)	0	1.03 (0.89–1.18)	0.714		
Antiretroviral naivety at M0*	41.5	0	0.86 (0.41–1.79)	0.683		
CD4 cell count <200 cells/mm^3 at M0*	33.9	0	0.88 (0.41–1.88)	0.749		
Detectable viral load at M0*	94.8	0.1	0.70 (0.17–2.94)	0.627		
CD4 cell count <200 cells/mm^3†	11.8	0	2.58 (0.99–6.75)	0.052	4.02 (1.45–11.1)	0.007
Detectable viral load†	40.2	0.03	1.24 (0.59–2.59)	0.574		

Continued

Table 3 Continued

	% of patients or mean (SD)	% of miss.data	Univariate analyses		Multivariate analysis	
			HR (95% CI)	p-value	AHR (95% CI)	p-value
Metabolic characteristics		1.6				
BMI categories*‡						
Underweight: <18.5 (ref)	5.8		1			
Normal weight: 18.5–24.9	72.8		0.65 (0.15–2.76)	0.556		
Overweight or obese: >25	19.8		0.57 (0.11–2.87)	0.498		
Hypertriglyceridaemia*‡	8.4	0	2.06 (0.79–5.37)	0.141	2.98 (1.11–8.01)	0.030
Hypercholesterolaemia*‡	6.5	0.1	0.95 (0.22–3.97)	0.939		
Personal history of CHD*‡	1.2	0	9.39 (2.22–39.8)	0.002		
Family history of CHD*‡	28.0	0	1.82 (0.89–3.71)	0.102	2.25 (1.08–4.71)	0.031
Personal history of hypertension*‡	6.1	0	2.73 (1.05–7.13)	0.040		

(A)HR, (adjusted) HR; ART, antiretroviral therapy; CADE, coronary or other arterial disease event; CHD, coronary heart disease.
*Fixed variable (measured at M0, M1 or M12);
†Time-varying variable (the last available value before each visit); percentages and averages are computed on all follow-up visits for time-varying variables;
‡At M12;
§Percentages and averages are computed at the end of the follow-up (last available visit for each patient);
¶Depressive symptoms: the Centre for Epidemiologic Studies Depression Scale (CES-D) score is >17 for men and >23 for women.

was 37.7 (9.5) years and approximately one-third of the patients had a secondary school certificate. Individuals HIV-infected through injecting drug use accounted for 18% of the study patients. At baseline, 44% of all the patients were ARV naive, half were in CDC stage A, more than three-quarters (80%) had not experienced opportunistic infections and 22% were coinfected with HCV. The selected patients had a detectable viral load at 43% of the follow-up visits, had a CD4 cell count <200 cells/mm^3 at 14% and reported depressive symptoms at 32% of the visits. The median (IQR) of CD4 cell count was 442 (284 to 633) cells/mm^3 during the follow-up. During the follow-up, more than half of the patients (63%) were highly adherent, and after 1 year of ART the median (IQR) number of self-reported symptoms excluding lipodystrophy was 4 (2 to 7), while this value was 1 (0 to 5) for lipodystrophy symptoms. Only 16% of the patients declared smoking more than 20 cigarettes/day during the cohort follow-up. Nearly 19% of the patients reported they were alcohol abstainers, three-quarters reported moderate alcohol consumption (59% reporting less than 1 AU/day and 18% between 1 and 4(3) AU/day for men(women)), while only a minority of patients (4%) reported elevated alcohol consumption. As the two intermediate categories (≤1 AU/day; >1 and ≤4(3) AU/day for men(women)) had similar estimated adjusted HR (AHR) and p-values in both multivariate analyses, we decided to aggregate them for model parsimony.

In the subsample of patients with available metabolic data (table 3), the majority (73%) had a normal BMI, 17% were classified in the overweight category and a minority was classified in each of the two more extreme categories (6% underweight and 3% obese). About 8% of the patients had hypertriglyceridaemia and 6% had hypercholesterolaemia at M12. One year after the enrolment in the cohort, 6% of the patients reported a personal history of hypertension. Only 1% and 28%, respectively, had a personal and family history of CHD.

In the entire study group (n=1154), the following factors were found to be independent predictors of a major CADE: older age at baseline (AHR (95% CI)=1.07 (1.04 to 1.10)), tobacco consumption>20 cigarettes/day (4.19(2.17 to 8.11)) and CD4 cell count <200 cells/mm^3 (2.52(1.15 to 5.48)) (see table 2). In addition, a negative association was found between female gender and a major CADE (0.25(0.08 to 0.83)). After accounting for the effect of age, gender, tobacco consumption and CD4 cell count <200 cells/mm^3 in the multivariate Cox model, individuals with moderate alcohol consumption (≤4(3) AU/day for men(women)) were at a lower risk of a major CADE (0.38(0.20 to 0.71)), than alcohol abstainers, while those drinking more than 4(3) AU/day for men(women) were not significantly different from abstainers (p=0.229).

These results remained valid also when the analysis was restricted to the subgroup of patients with available metabolic data and the follow-up period M12–M132.

After adjusting for age, tobacco consumption, hypertriglyceridaemia and a family history of CHD, we consistently found a negative association between moderate alcohol use (0.23(0.11 to 0.49)), and a positive association between CD4 cell count <200 cells/mm^3 (4.02 (1.45 to 11.1)) and a major CADE after 1 year after enrolment (table 3).

No significant association was found between the time of exposure to different ARV drugs and a major CADE. No significant interaction was found between smoking habits and hypertriglyceridaemia or a personal history of CHD. Furthermore, detectable viral load was not associated with a major CADE in univariate or multivariate analyses.

For the Cox models fitted in this study, proportional hazards assumption remained valid, either globally and/or with respect to each covariate. The residual analysis did not alter the results of the multivariate model.

The sensitivity analyses performed first by excluding patients with a history of CHD (n=7), and then patients who died due to alcoholic cirrhosis (n=6), confirmed the same pattern of risk factors observed for the entire population. The other sensitivity analyses, performed separately on the subgroups of patients with HCV coinfection and on those not coinfected with HCV, revealed the same effect of alcohol consumption on CADE, although some variables among the other factors were less significant for the coinfected patients (results not shown, available on request).

DISCUSSION

This longitudinal study clearly confirms that in ARV-treated individuals, proximal CD4 cell count lower than 200 cells/mm^3 remains a risk factor associated with a major coronary and other arterial disease events. This result remains valid even after adjustment for metabolic disorders such as hypertriglyceridaemia and a family history of CHD, the strength of the association remaining unchanged.

The relationship between CADE and CD4 cell count, in addition to the lack of association between CADE and specific ARV classes, confirms previous results[7] where the association between exposure to certain ARV and CADE was no longer evident after controlling for traditional risk factors and HIV-disease markers. Indeed, the association between specific ARV drugs and a major CADE, like myocardial infarctus, has been shown in very powerful studies,[5] where adjustment for nadir CD4 lymphocyte count or peak HIV-1 RNA level did not modify the results. However, in the study cited, no adjustment for proximal CD4 cell count was performed, and the association with the class of ARV became weaker after adjustment for serum lipid levels.[5] Indeed, although ART may modify lipid levels and increase the risk of a CADE, it may also reduce this risk by reducing HIV-associated inflammation following a long-term suppression of HIV replication.[43] The lack of association with exposure to some specific ARV classes in the present study, factors that are usually associated with an increased risk of CADE,[44 45] suggests that reduced immunological response to ART over a long follow-up, as well as known CADE-risk factors may have a more important impact than exposure to a specific ARV drug.

It is also possible that patients with altered lipid profiles were switched to other classes of ARV drugs during the follow-up. As a consequence, in the long term, CD4 cell count <200 cells/mm^3 remains a correlate of an increased risk of CADE, whatever the ARV received.

In our study, individuals reporting elevated alcohol consumption exhibited the same risk of a CADE as alcohol abstainers. In contrast, those reporting moderate alcohol consumptions had a lower risk. This result was confirmed after adjustment for additional risk factors including tobacco use, age, gender and CD4 cell count. This relationship between alcohol consumption and a CADE remained significant and J-shaped, even after adjustment for data on metabolic risk factors such as having a history of CHD and hypertriglyceridaemia, which were available for a subset of patients. As highlighted in previous observations in the general population[28 46–49] and certain populations affected by other diseases,[50] these results confirmed that the increased risk of a CADE in HIV-infected patients receiving ART is not attributable to an elevated alcohol use. Furthermore, we highlighted the apparent protective effect of moderate alcohol consumption in ART-treated HIV-infected patients.

It is important to note that after the introduction of ART in 1996, the sudden decrease observed in HIV-related mortality was nonetheless accompanied by a relative increase of non-HIV-based mortality as a part of the total mortality of HIV-infected patients,[51] cardiovascular diseases becoming increasingly important. This increase can be explained first by a reduction in the competing role of HIV-related mortality, which, in the long term, was much more detrimental to health than other causes of deaths. Second, the high prevalence in this population of other risk factors like tobacco use, together with ART-related morbidity including altered lipid profiles and triglycerides, may contribute to an increased risk of a CADE.

The association found in our study between moderate alcohol use and a reduced CADE risk is not consistent with all previous research in HIV-infected patients. Freiberg *et al*[26] pointed out that among HIV-infected men in the US, hazardous drinking and both alcohol abuse and dependence were associated with a higher prevalence of cardiovascular disease compared with infrequent and moderate drinking, even after adjusting for traditional risk factors, ARV therapy and CD4 cell count. This difference in the results may be due to the different design of the two studies (longitudinal for ours versus cross-sectional for Freiberg's), but probably also to the different types of alcohol mainly consumed in the two populations, red wine consumption being more

widespread in France than in the US. This difference in the pattern of alcohol use has already been highlighted in a comparative study on cardiovascular disease in non HIV-infected Irish and French males, showing an increased protective effect of drinking red wine in the latter population.[52] An increased wine consumption probably brings about an increase in high-density lipoprotein (HDL) cholesterol levels, which helps protect against cardiovascular events. On the other hand, beer and spirit consumption are linked to increased triglyceride levels.[53] We do not know to what extent moderate alcohol users are representative of a population with a better health status as alcohol use in France is relatively frequent in the general population and this fact may increase the strength of the association found.

Another possible hypothesis is that excessive alcohol consumption can increase inflammatory markers' levels,[54] which in turn probably leads to a higher risk of CADE and premature ageing in HIV patients. However, this hypothesis was not demonstrated in a study conducted in older adults without a cardiovascular disease, where alcohol intake was found to be associated with lower levels of inflammatory markers.[55] In the meantime it is important to remember that individuals with immune suppression are at a greater risk of cancer, a disease whose pattern of risk factors also include alcohol use, even when moderate.[56]

Tobacco smoking has consistently been found to be a major risk factor for a cardiovascular disease.[57] Smoking prevalence and dependence in HIV-infected patients is higher than that in the general population.[58] Effective interventions for reducing and quitting smoking,[59] especially for patients with several risk factors, are strongly recommended especially considering the increased cardiovascular risk which exists in HIV-infected smokers receiving ART.[60] However, results from studies reporting the effectiveness of interventions for quitting smoking in HIV-infected individuals are inconsistent.[61]

It is worth noting the lack of association between hypercholesterolaemia and the risk of a CADE in our study. This result suggests that HIV physicians need to be cautious about basing clinical decisions merely upon measured lipid levels in HIV-infected patients. Other risk factors, including behavioural ones, deserve a greater consideration for clinical management.

Some limitations of this study need to be acknowledged. First, our definition of CADE includes different types of events which might not share the same pattern of risk factors. However, an additional analysis performed on a restricted dataset and which adjusted for other potential risk factors (such as hypertriglyceridaemia) confirmed the pattern found in the main analysis.

Second, information on alcohol use was mainly based on self-reports and these may tend to underestimate alcohol consumption. However, it has been reported that HIV–HCV coinfected patients tend to under-report alcohol use more to their hepathologist than to other physicians.[62] As our patients were all followed-up by HIV physicians, it is likely that the degree of under-reporting did not greatly affect HRs' estimates. Moreover, the association found between the excessive alcohol consumption and the biomarkers of alcoholic liver injury indicate a good accuracy of self-reported data on alcohol consumption.

Then, the fact that excessive alcohol users exhibit similar HRs to abstainers may be also attributable to the two following reasons. First, some individuals with excessive alcohol consumption may have died due to a liver failure before experiencing a cardiovascular event and this could have reduced the impact of excessive alcohol use on CADE. However, when we performed a sensitivity analysis excluding patients who died due to alcoholic cirrhosis, the results remained unchanged. Second, a proportion of abstainers may have been past (heavy) alcohol users and may have had to stop drinking for health reasons. Unfortunately, we do not have information about alcohol use before the beginning of the cohort, or about diagnosis of alcoholism or reasons for quitting alcohol.

Finally, it would have been interesting to compute the Framingham risk score[61] and use it as a covariate in the multivariate model. Unfortunately, as our study was not initially designed to thoroughly assess the impact of all possible CHD risk factors, some of the variables used in the construction of this score (such as treated and untreated systolic blood pressures, as well as total and HDL cholesterol) were not available during the first two years of our study. Moreover, our results showed a different pattern of factors than those found in the Framingham study (some of the traditional risk factors, such as BMI and hypercholesterolaemia, were not significant), so using this score would have been less informative than using all the factors separately.

It is surprising that the classical risk factor hypercholesterolaemia was not found to be associated with a CADE risk in this study. This may be due to the fact that rather the low-density lipoprotein cholesterol and/or the total/HDL cholesterol quotient may be predictors of CADE risk but not total cholesterol. Unfortunately, the complete data regarding cholesterol levels were not available during the first 2 years of our study, and therefore, these factors could not be assessed in this analysis.

This cohort is representative of the first generation of patients receiving potent ART. As the cardiovascular diseases are rising issue in all HIV-infected populations receiving ART, these results can give important information about the pattern of risk and protective factors in all treated HIV-infected populations.

In conclusion, in the long term, absence of immunodepression and moderate alcohol consumption remain associated with a lower risk of a major CADE. Combined interventions to reduce CADE-risk-related behaviours including adherence counselling to assure long-term immunological response to ART in HIV-infected individuals are now a clinical and public health priority.

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