

High-density lipoprotein-cholesterol levels and risk of cancer in HIV-infected subjects

Data from the ICONA Foundation Cohort

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Abstract

Investigation of the relationship between high-density lipoprotein-cholesterol (HDL-c) and the risk of developing cancer in a prospective cohort of human immunodeficiency virus (HIV)-infected patients.

The Italian Cohort of Antiretroviral-naïve Patients Foundation Cohort is an Italian multicenter observational study recruiting HIV-positive patients while still antiretroviral treatment-naïve, regardless of the reason since 1997.

Patients with at least 1 HDL-c value per year since enrollment and one such value before antiretroviral treatment initiation were included. HDL-c values were categorized as either low (<39 mg/dL in males or <49 mg/dL in females) or normal. Cancer diagnoses were classified as AIDS-defining malignancies (ADMs) or non-AIDS-defining malignancies (NADMs). Kaplan–Meier curves and Cox proportional-hazards regression models were used.

Among 4897 patients (13,440 person-years of follow-up [PYFU]), 104 diagnoses of cancer were observed (56 ADMs, 48 NADMs) for an overall incidence rate of 7.7 (95% confidence interval [CI] 6.3–9.2) per 1000 PYFU.

Low HDL-c values at enrollment were associated with higher risk both of cancer (crude hazard ratio [HR] 1.72, 95% CI 1.16–2.56, $P=0.007$) and of NADM (crude HR 2.50, 95% CI 1.35–4.76, $P=0.003$). Multivariate analysis showed that the risk of cancer diagnosis was higher in patients with low HDL-c values (adjusted HR [AHR] 1.87, 95% CI 1.18–2.95, $P=0.007$) in older patients, those patients more recently enrolled, and in those with low current cluster of differentiation 4+ levels, and/or high current HIV-ribonucleic acid.

The multivariate model confirmed an association between HDL-c (AHR 2.61, 95% CI 1.40–4.89, $P=0.003$) and risk of NADM. Low HDL-c is an independent predictor of cancer in HIV-1-infected subjects.

Abbreviations: ABCA-1 = ATP-binding cassette transporter A1, ADMs = AIDS-defining malignancies, AHR = adjusted hazard ratio, AIC = Akaike information criterion, AIDS = acquired immune deficiency syndrome, ApoA1 = apolipoprotein A1, ART = antiretroviral treatment, TNF- α = tumor necrosis factor- α , CD4 = cluster of differentiation 4, CD8 = cluster of differentiation 8, HBSAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV-Ab = hepatitis C virus antibody, HDL-c = high-density lipoprotein-cholesterol, HIV = human immunodeficiency virus, HIV-RNA = HIV-ribonucleic acid, HPV = human papillomavirus, HR = hazard ratio, ICONA = Italian Cohort of Antiretroviral-naïve Patients, IQR = interquartile range, IR = incidence rate, KS = Kaposi sarcoma, LDL-c = low-density lipoprotein cholesterol, nadir = lowest ever, NADMs = non-AIDS-defining malignancies, PYFU = person-years of follow-up, SAS = statistical analysis system, VL = viral load.

Keywords: AIDS-defining malignancies, cancer, HDL, HIV, non-AIDS-defining malignancies

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1. Introduction

Cancer is one of the most important causes of mortality in human immunodeficiency virus (HIV)-infected patients, occurring both as acquired immune deficiency syndrome (AIDS)-defining malignancies (ADMs) and non-AIDS-defining malignancies (NADMs).^[1,2]

Inflammation is a crucial pathogenetic mechanism involved in cancer development,^[3] and inflammation and immune activation are highly prevalent in HIV-infected subjects despite the use of antiretroviral treatment (ART).^[4,5]

Lipid profile is profoundly influenced by proinflammatory state, which alters predominantly high-density lipoprotein-cholesterol (HDL-c) composition and function.^[6,7] Indeed, low HDL-c has been associated with high levels of tumor necrosis factor- α (TNF- α)^[8] and predominance of a proinflammatory phenotype in monocyte-derived macrophages, suggesting that inflammation could be a risk factor for low HDL-c.^[9]

Of late, low HDL-c values have been associated with cancer diagnosis.^[10,11] Meanwhile, apolipoprotein A1 (ApoA1), an important component of HDL-c, has been demonstrated to have a direct suppressive effect on tumor cells of melanoma *in vitro* and *in vivo*.^[12] This predominant role of ApoA1 was confirmed by studies that used ApoA1 HDL-c-mimetics peptides to inhibit ovarian and colon cancer development in mouse models.^[13,14]

Little is known about the predictive value of HDL-c in cancer development in the setting of HIV infection.

HIV affects the ATP-binding cassette transporter A1 (ABCA1)-dependent cholesterol efflux through Nef protein, reducing ApoA1 and, consequently, lowering HDL-c serum level.^[15]

Baker et al^[16] demonstrated that both HDL-c and ApoA1 increase after the start of ART introduction, at levels which correspond to the degree of inflammation present at entry, suggesting that activation of inflammation pathways contribute to HIV-associated changes in HDL-c.

Cancer risk has also been shown to undergo changes during ART depending on cluster of differentiation 4 (CD4) cell count and HIV viral load (VL) modification.

To shed light on the processes described above, the primary aim of our study was to evaluate the association between HDL-c levels and the development of ADM and NADM in a large cohort of HIV-infected patients initiating ART in Italy.

2. Methods

2.1. Study design and participants

This is a cohort study of all the HIV-1-infected subjects enrolled in the Italian Cohort of Antiretroviral-Naïve Patients (ICONA) Foundation Cohort Study with at least 1 HDL-c value per year available since enrollment and 1 such value before ART initiation. As annual monitoring of HDL-c is a more recent practice, only subjects enrolled in the cohort since January 2009 were eligible for this study.

The ICONA Foundation Cohort is a cohort of HIV-infected patients which superseded the original ICONA study (see detailed description of this cohort elsewhere),^[17] recruiting HIV-positive patients while still ART-naïve, regardless of the reason. On average, CD4 cell counts, HIV VL and other laboratory parameters are measured, and clinical and therapeutical data are collected every 4 months.

Incident cancer cases diagnosed after enrollment were considered in the analyses, focusing on the earliest cancer diagnosis and ignoring subsequent diagnoses in the same patient.

Prevalent cases, that is, patients with a cancer diagnosis before enrollment in the ICONA Foundation Cohort, were excluded from the analyses.

Malignancies were classified as ADM or NADM; ADM included Kaposi sarcoma (KS), non-Hodgkin lymphoma, primary central nervous system lymphoma, and invasive cervical cancer; NADM included Hodgkin lymphoma, hepatocellular carcinoma (HCC), lung cancer, larynx cancer, anal cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, melanoma, breast cancer, prostate cancer, testicular cancer, bladder cancer, pancreas cancer, and renal cancer.

Patients were followed up from enrollment date to earliest cancer diagnosis, latest clinical visit, or lost-to-follow-up or death. Data freezing for this analysis was June 2015.

2.2. Statistical analysis

Results were described as median (interquartile range [IQR]) or frequency (%), unless otherwise specified.

High-density lipoprotein-cholesterol was used either as a continuous variable or as a categorical variable in one of the 2 classes: low (<39 mg/dL in males or <49 mg/dL in females) or normal. Our analysis factored in not only the last HDL-c value taken before cancer diagnosis, but each HDL-c value collected over the entire study period.

Crude rates of incident cancer (incidence rate [IR]) were calculated as the number of cancer diagnoses divided by the number of person-years of follow-up (PYFU), and were expressed per 1000 PYFU; confidence intervals (CIs) for the rates were calculated assuming a Poisson distribution.

The Kaplan–Meier method was used to estimate the probability of cancer occurrence based on HDL-c level at enrollment; curves were compared by use of the log-rank test.

Three multivariate Cox proportional-hazards regression models were used to evaluate the association between HDL-c and the risk of cancer, and the risk of specific cancer categories (ADM and NADM), adjusting for a number of potential confounders.

At univariate analysis, we determined if HDL-c was better modeled as a continuous variable or as a categorical variable (low vs normal), based on the Akaike information criterion (AIC). As the estimated AICs were very similar (1–2 points AIC difference, with no clear evidence of one model's superiority), HDL-c was considered to be a categorical variable in the 3 multivariate models.

Factors included in the multivariate models were either fixed (age, sex, smoke, hepatitis C virus-antibody [HCV-Ab], hepatitis B surface antigen [HBsAg], lowest ever [nadir] CD4, calendar year of enrollment) or time-updated variables (use of ART, current CD4, current HIV-ribonucleic acid [HIV-RNA] [on the log₁₀ scale], current HDL-c, and current triglycerides).

Missing values of categorical variables were grouped into specific categories, with no loss of observations at multivariate analysis. Missing values of continuous variables, on the other hand, led to a loss of observations, at which point the number of events (on average 88%) effectively retained in each multivariate model was indicated.

The multivariate models were refit after additional testing of current CD4/cluster of differentiation 8 (CD8) ratio, a known predictive factor of non-AIDS-related events.^[18] The multivariate analyses were also restricted to that subgroup of patients exposed to ART, and inclusion in the analyses of cancer was restricted to those cancer diagnoses which were performed subsequent to

ART initiation. Finally, multivariate analyses were recalculated after exclusion of cancer diagnoses recorded within the first 6 months since enrollment, to exclude those diagnoses which might be considered prevalent, rather than incident events.

All reported *P* values were 2-sided and considered to be statistically significant if below 0.05. The analyses were performed using statistical analysis system (SAS) Software, release 9.2 (SAS Institute, Cary, NC).

2.3. Ethics

All patients signed consent forms to participate in the ICONA Foundation Study, in accordance with the ethics standards of the committee on human experimentation and the Helsinki Declaration (1983 revision).

3. Results

In all, 4897 patients participated. Demographics and clinical characteristics are shown in Table 1.

Overall median age was 37 years (31–45), 22% were females, 20% were non-Italian subjects, and 41% were smokers; HIV transmission was mainly by homosexual intercourse (43%). An AIDS diagnosis before enrollment occurred in 10% of patients and CD4+ nadir was 320 (186–454) cells/mm³. Very few patients had a positive serologic test for HCV-Ab (9%) and for HBsAg (3%). Median time of follow-up was 1.9 (0.42–3.93) years, accounting for 13,440 PYFU (with incident cancer: 0.96 [0.22–2.29] years; without incident cancer: 1.92 [0.44–3.97] years; *P*=0.001). During follow-up, 104 diagnoses of cancer were reported (56 ADMs and 48 NADMs); cancer characteristics are depicted in Table 2.

Forty-eight per cent of cancers occurred 12 months after enrollment and 80% of cancers were diagnosed after ART initiation. KS (64%) was the most frequent ADM followed by non-Hodgkin lymphoma (23%) and cervical cancer (13%). Hodgkin lymphoma (21%) was the most frequent NADM followed by lung and bladder cancer (for both 15%) and liver cancer (8%).

At enrollment, 2448 (50%) subjects had low HDL-c values, and the median number of the available HDL-c determinations during follow-up was 5 (2–10).

Patients with low as opposed to normal HDL-c values at enrollment were less frequently male (77% vs 80%; *P*=0.004), more frequently smokers (47% vs 43%; *P*=0.006), with a previous diagnosis of AIDS (12% vs 7%; *P*<0.001), started ART during follow-up (79% vs 69%; *P*<0.001), were older (38 [31–46] vs 36 [30–44] years; *P*<0.001), with lower CD4 nadir (288 [141–432] vs 348 [235–480] cells/mm³; *P*<0.001), lower CD4+ cell count (351 [164–534] vs 449 [293–618] cells/mm³; *P*<0.001), lower CD4/CD8 ratio (0.35 [0.19–0.57] vs 0.47 [0.30–0.69]; *P*<0.001), higher HIV-VL (4.74 [4.07–5.36] vs 4.39 [3.67–4.92] log₁₀copies/mL; *P*<0.001), lower total lymphocytes count (1765 [1200–2370] vs 1900 [1440–2400] cells/mm³; *P*<0.001), lower total cholesterol (151 [127–177] vs 174 [152–200] mg/dL; *P*<0.001), lower low-density lipoprotein-cholesterol (LDL-c) (92 [72–114] vs 104 [84–126] mg/dL; *P*<0.001), and higher triglycerides (124 [88–174] vs 88 [66–124] mg/dL; *P*<0.001). Patients with low HDL-c values at enrollment also died more frequently during follow-up (2.8% vs 1.5%; *P*=0.002) as compared with those with normal HDL-c values.

The overall cancer incidence rate was 7.7 (95% CI 6.3–9.2) per 1000 PYFU (ADM: 4.2 [95% CI 3.1–5.3] per 1000 PYFU; NADM: 3.6 [95% CI 2.6–4.6] per 1000 PYFU).

Overall and NADM incidence rates significantly differed between subjects with normal as opposed to those with low values of HDL-c at enrollment (overall: 5.7 [95% CI 4.2–7.8] vs 9.8 [95% CI 7.7–12.6] per 1000 PYFU; *P*=0.006 by univariate Poisson regression; ADM: 3.7 [95% CI 2.5–5.4] vs 4.7 [95% CI 3.3–6.7] per 1000 PYFU; *P*=0.353 by univariate Poisson regression; NADM: 2.0 [95% CI 1.2–3.5] vs 5.2 [95% CI 3.7–7.2] per 1000 PYFU; *P*=0.002 by univariate Poisson regression).

Patients with incident cancer as compared with those without (Table 1) were found to be older (45 [37–53] vs 37 [31–45] years; *P*<0.001), more frequently with previous diagnosis of AIDS (65 [62%] vs 399 [8%] events; *P*<0.001), with lower CD4 nadir (179 [66–277] vs 324 [190–457] cells/mm³; *P*<0.001), earlier calendar year of enrollment (2009 [2006–2011] vs 2011 [2008–2013]; *P*<0.001), lower CD4 cell count (220 [85–472] vs 407 [237–580] cells/mm³; *P*<0.001), lower CD4/CD8 ratio (0.26 [0.14–0.56] vs 0.42 [0.25–0.63]; *P*<0.001), lower total lymphocytes count (1460 [1006–2093] vs 1820 [1320–2400] cells/mm³; *P*<0.001), higher HIV-VL (4.91 [3.95–5.43] vs 4.56 [3.83–5.14] log₁₀copies/mL; *P*=0.011), and lower HDL-c (35 [28–46] vs 40 [33–49] mg/dL; *P*=0.001) at enrollment.

Low HDL-c values at enrollment were associated with a higher risk of any type of cancer (crude hazard ratio [HR] 1.72, 95% CI 1.16–2.56, *P*=0.007) and with a higher risk of NADM (crude HR 2.50, 95% CI 1.35–4.76, *P*=0.003) as shown in Fig. 1.

At univariate analysis (Table 3), the risk of cancer was associated with older age, not being on ART, low CD4 values, low CD4/CD8 ratio, high HIV-RNA values, low total cholesterol values, low HDL-c values, low LDL-c values, and high values of fasting glucose.

Results of the multivariate analysis are reported in Table 4. Notably, the risk of cancer diagnosis was higher in patients with low current HDL-c values (adjusted HR [AHR] for low vs normal: 1.87, 95% CI 1.18–2.95, *P*=0.007) and in those with older age (AHR per 5-years older: 1.32, 95% CI 1.20–1.44, *P*<0.001), low current CD4 levels (AHR per 100 cells/mm³ higher: 0.78, 95% CI 0.68–0.91, *P*<0.001), high current HIV-RNA values (AHR per 1 log₁₀copies/mL higher: 1.69, 95% CI 1.36–2.11, *P*<0.001), and more recent calendar year of enrollment (AHR per 1 more recent year: 1.10, 95% CI 1.03–1.17, *P*=0.005).

Low values of HDL-c still appeared to be a risk factor for risk of ADM (Table 4), although not statistically significant (AHR for low vs normal: 1.28, 95% CI 0.66–2.49, *P*=0.475); older age (AHR per 5 years older: 1.16, 95% CI 1.02–1.33, *P*=0.029), low nadir CD4 levels (AHR per 100 cells/mm³ higher: 0.68, 95% CI 0.50–0.92, *P*=0.011), high current HIV-RNA values (AHR per 1 log₁₀copies/mL higher: 2.27, 95% CI 1.70–3.06, *P*<0.001), and more recent calendar year of enrollment (AHR per 1 more recent year: 1.19, 95% CI 1.08–1.31, *P*<0.001) were associated with a higher risk of ADM.

The multivariate model on risk of NADM confirmed associations with low values of HDL-c (AHR for low vs normal: 2.61, 95% CI 1.40–4.89, *P*=0.003), older age (AHR per 5 years older: 1.50, 95% CI 1.31–1.72, *P*<0.001), and low current CD4 levels (AHR per 100 cells/mm³ higher: 0.73, 95% CI 0.60–0.89, *P*=0.002).

Additional adjustment for current CD4/CD8 ratio (see Table 5) led to similar conclusions with regard to the effect of low HDL-c values (AHR of any cancer for low vs normal: 1.87, 95% CI

Table 1**Demographic, clinical, and laboratory characteristics of human immunodeficiency virus-infected patients in the Italian cohort of antiretroviral-naïve patients cohort according to cancer occurrence.**

Characteristic	All patients (N=4897)	Patients with incident cancer (n=104)	Patients without incident cancer (n=4793)	P	Patients with incident ADM (n=56)	Patients with incident NADM (n=48)
Age, y	37 (31–45)	45 (37–53)	37 (31–45)	<0.001*	45 (36–50)	47 (41–55)
Males	3841 (78%)	84 (81%)	3757 (78%)	0.631†	44 (83%)	40 (83%)
Nationality				0.026†		
Italian	3903 (80%)	92 (88%)	3811 (80%)		47 (84%)	45 (94%)
Non-Italian	994 (20%)	12 (12%)	982 (20%)		9 (16%)	3 (6%)
Smoke				0.466†		
Current/ex	2009 (41%)	47 (45%)	1962 (41%)		24 (43%)	23 (48%)
No	2423 (50%)	48 (46%)	2375 (50%)		28 (50%)	20 (42%)
Unknown	465 (9%)	9 (9%)	456 (9%)		4 (7%)	5 (10%)
Body mass index, kg/m ²	22.4 (19.4–24.7)	21.5 (18.5–24.0)	22.5 (19.4–24.7)	0.132*	21.7 (20.0–23.9)	22.9 (19.7–24.9)
HIV transmission risk				0.818†		
IDU	474 (10%)	11 (11%)	463 (10%)		4 (7%)	7 (15%)
MSM	2114 (43%)	44 (42%)	2070 (43%)		28 (50%)	16 (33%)
Heterosexual	1941 (40%)	40 (39%)	1901 (40%)		20 (36%)	20 (42%)
Other/unknown	368 (7%)	9 (9%)	359 (7%)		4 (7%)	5 (10%)
HCV-Ab				0.598†		
Positive	449 (9%)	11 (11%)	438 (9%)		3 (5%)	8 (17%)
Negative	3038 (62%)	63 (61%)	2975 (62%)		39 (70%)	24 (50%)
Unknown	1410 (29%)	30 (29%)	1380 (29%)		14 (25%)	16 (33%)
HBsAg				0.165†		
Positive	160 (3%)	6 (6%)	154 (3%)		1 (2%)	5 (10%)
Negative	3241 (66%)	69 (66%)	3172 (66%)		42 (75%)	27 (56%)
Unknown	1496 (31%)	29 (28%)	1467 (31%)		13 (23%)	16 (33%)
Diagnosis of AIDS				<0.001†		
Yes	464 (10%)	65 (62%)	399 (8%)		56 (100%)	9 (19%)
No	4433 (90%)	39 (38%)	4394 (92%)		0	39 (81%)
Nadir CD4, cells/mm ³	320 (186–454)	179 (66–277)	324 (190–457)	<0.001*	99 (40–241)	222 (127–323)
Calendar year of enrollment				<0.001*		
2011 (2009–2013)	2011 (2009–2013)	2009 (2006–2011)	2011 (2008–2013)		2010 (2007–2013)	2007 (2004–2010)
2010 (2006–2012)	2010 (2006–2012)	2007 (2002–2010)	2010 (2006–2012)		<0.001*	2006 (2002–2009)
Number of patients who started ART				<0.001†		
3603 (74%)	3603 (74%)	101 (97%)	3502 (73%)		55 (98%)	46 (96%)
Calendar year of ART initiation				<0.001*		
2011 (2009–2013)	2011 (2009–2013)	2009 (2007 (2011))	2011 (2009–2013)		2010 (2007–2012)	2008 (2005–2010)
Months to ART initiation since enrollment	0.82 (0.07–6.94)	0.49 (0.07–5.07)	0.86 (0.07–6.94)	0.162*	0.43 (0–5.07)	0.61 (0.07–7.07)
Months of ART	23.1 (7.3–44.9)	4.1 (0.2–16.1)	23.8 (7.8–45.2)	<0.001*	1.4 (0.2–8.6)	11.5 (3.7–29.5)
Use of statin during follow-up†				0.327†		
55 (1%)	55 (1%)	2 (2%)	53 (1%)		0	2 (4%)
Use of fenofibrate during follow-up‡				0.999†		
5 (0.1%)	5 (0.1%)	0	5 (0.1%)		0	0
CD4, cells/mm ³	404 (229–579)	220 (85–472)	407 (237–580)	<0.001*	128 (46–409)	263 (172–521)
CD4%	22.2 (14.8–29.0)	15.7 (9.0–27.0)	22.3 (15.0–29.0)	<0.001*	13.9 (6.0–23.2)	20.0 (12.4–29.0)
CD8, cells/mm ³	881 (619–1254)	812 (573–1043)	884 (621–1258)	0.023*	816 (531–1076)	812 (589–963)
CD8%	53.0 (44.2–62.0)	54.0 (45.3–67.0)	53.0 (44.1–62.0)	0.046*	58.1 (49.0–71.0)	50.6 (44.8–59.0)
CD4/CD8 ratio	0.41 (0.24–0.63)	0.26 (0.14–0.56)	0.42 (0.25–0.63)	<0.001*	0.21 (0.08–0.43)	0.33 (0.22–0.71)
HIV-RNA, log ₁₀ copies/mL	4.56 (3.83–5.15)	4.91 (3.95–5.43)	4.56 (3.83–5.14)	0.011*	5.03 (4.71–5.49)	4.46 (3.50–5.24)
Total cholesterol, mg/dL	164 (138–189)	168 (130–193)	164 (139–189)	0.986*	170 (125–199)	163 (134–191)
HDL-c, mg/dL	40 (33–49)	35 (28–46)	40 (33–49)	0.001*	37 (30–49)	35 (28–43)
Normal§	2449 (50%)	39 (38%)	2409 (50%)		25 (45%)	14 (29%)
Low§	2448 (50%)	65 (62%)	2384 (50%)	0.013†	31 (55%)	34 (71%)
Number of HDL-c determinations during follow-up	5 (2–10)	3 (2–7)	5 (2–10)	0.005*	3 (1–5)	5 (2–11)
LDL-c, mg/dL	99 (77–120)	96 (70–125)	99 (78–120)	0.353*	87 (58–126)	99 (75–123)
Triglycerides, mg/dL	103 (75–152)	116 (88–161)	103 (74–151)	0.024*	114 (86–153)	124 (92–167)
Fasting glucose, mg/dL	86 (79–93)	87 (78–98)	86 (79–93)	0.421*	86 (80–96)	90 (77–100)
Total lymphocytes, 10 ⁶ cells/mm ³	1811 (1310–2400)	1460 (1006–2093)	1820 (1320–2400)	<0.001*	1390 (1000–2070)	1488 (1011–2095)

All variables were measured at enrollment, unless otherwise specified.

Data reported as median (IQR) or n (%).

ADM= AIDS-defining malignancies, AIDS= acquired immune deficiency syndrome, ART= antiretroviral treatment, CD4= cluster of differentiation 4, CD8= cluster of differentiation 8, HBsAg= hepatitis B surface antigen, HCV-Ab= hepatitis C virus-antibody, HDL-c= high-density lipoprotein-cholesterol, HIV= human immunodeficiency virus, HIV-RNA= HIV-ribonucleic acid, IDU= intravenous drug user, LDL-c= low-density lipoprotein-cholesterol, MSM= men who have sex with men, nadir= lowest ever, NADMs= non-AIDS-defining malignancies.

* By Wilcoxon rank-sum test.

† By chi-square or Fisher exact test, as appropriate.

‡ Use of statin or fenofibrate had to precede cancer, if occurred.

§ A low HDL value was defined as an HDL value outside the normal range, that is, <39 mg/dL in males or as an HDL value <49 mg/dL in females; a normal HDL value was defined as an HDL value within normal range, that is, ≥39 mg/dL in males or as an HDL value ≥49 mg/dL in females.

Table 2
Cancer characteristics (first diagnosis).

Characteristic	Any type (n=104)	ADM (n=56)	NADM (n=48)	P
Time to cancer occurrence, mos	11.5 (2.6–27.5)	4.4 (1.0–18.2)	16.0 (7.2–34.3)	0.001*
Distribution of cancer occurrence during follow-up				0.001*
≤3 mos	28 (27%)	24 (43%)	4 (8%)	
3.01–6 mos	14 (14%)	7 (13%)	7 (15%)	
6.01–<12 mos	12 (12%)	3 (5%)	9 (19%)	
≥12 mos	50 (48%)	22 (39%)	28 (58%)	
Number of HDL-c determinations according to cancer occurrence during follow-up				<0.001*
≤3 mos	1 (1–2)	1 (1–2)	1 (1–2)	
3.01–6 mos	2 (2–2)	2 (1–2)	2 (2–2)	
6.01–<12 mos	3 (2–4)	3 (3–3)	3 (2–4)	
≥12 mos	6 (4–13)	5 (3–9)	8 (5–13)	
Occurrence according to ART exposure				0.088†
Before or at ART start	21 (20%)	15 (27%)	6 (13%)	
After ART start	83 (80%)	41 (73%)	42 (88%)	
Type of malignancy				
AIDS-defining				
Non-Hodgkin lymphoma	13	13	10	
Kaposi sarcoma	36	36	4	
Cervical cancer	7	7	7	
Non-AIDS-defining			1	
Hodgkin lymphoma	10		3	
Hepatocellular carcinoma	4		1	
Lung cancer	7		1	
Larynx cancer	1		1	
Anal cancer	3		3	
Stomach cancer	1		3	
Colon cancer	1		2	
Rectal cancer	1		2	
Skin cancer	3		1	
Melanoma	3		7	
Breast cancer	2		1	
Prostate cancer	2		1	
Testicular cancer	1			
Bladder cancer	7			
Pancreas cancer	1			
Renal cancer	1			
Death for any cause	22 (21%)	8 (14%)	14 (29%)	0.091†

ADMs = AIDS-defining malignancies, AIDS = acquired immune deficiency syndrome, ART = antiretroviral treatment, HDL-c = high-density lipoprotein-cholesterol, NADMs = non-AIDS-defining malignancies.

* By Wilcoxon rank-sum test.

† By chi-square test.

1.14–3.06, $P=0.013$; AHR of ADM for low vs normal: 1.19, 95% CI 0.56–2.52, $P=0.648$; AHR of NADM for low vs normal: 2.65, 95% CI 1.38–5.08, $P=0.003$] with a weak association with CD4/CD8 ratio.

Among patients who had received ART (see Table 6), the independent association between HDL-c and post-ART cancer occurrence of any type or NADM was confirmed (AHR of any cancer for low vs normal: 2.39, 95% CI 1.44–3.96, $P<0.001$; AHR of ADM for low vs normal: 1.62, 95% CI 0.75–3.48, $P=0.221$; AHR of NADM for low vs normal: 3.14, 95% CI 1.59–6.21, $P=0.001$); among the other factors evaluated in the model, the protective effect of a longer exposure to ART on the risk of cancer became also evident in all the 3 models (AHR of any cancer per 1 month longer: 0.94, 95% CI 0.93–0.95, $P<0.001$; AHR of ADM per 1 month longer: 0.94, 95% CI 0.92–0.95, $P<0.001$; AHR of NADM per 1 month longer: 0.94, 95% CI 0.93–0.96, $P<0.001$).

Finally, we refit the multivariate models after exclusion of cancer diagnoses occurred within the first 6 months since enrollment: current HDL-c remained an independent predictor

of any type of cancer or NADM (AHR of any cancer for low vs normal: 1.82, 95% CI: 1.05–3.17, $P=0.033$; AHR of ADM for low vs normal: 1.15, 95% CI 0.47–2.81, $P=0.753$; AHR of NADM for low vs normal: 2.51, 95% CI 1.23–5.11, $P=0.012$).

4. Discussion

In a large cohort of ART-naïve patients seen for care in Italy, our primary goal was to evaluate the role of HDL-c levels as a risk factor for cancer, both ADM and NADM.

In our study, we found low HDL-c (<39 for men and <49 for women) to be an independent risk factor for cancer in HIV, especially for NADM. Indeed, HIV-infected patients with low HDL-c are at 87% more risk of developing malignancies, and at more than double the risk of developing NADMs.

The HDL-c possesses multiple anti-inflammatory properties, such as inhibition of chemoattractant molecules and reduction of expression of adhesion molecules.^[19]

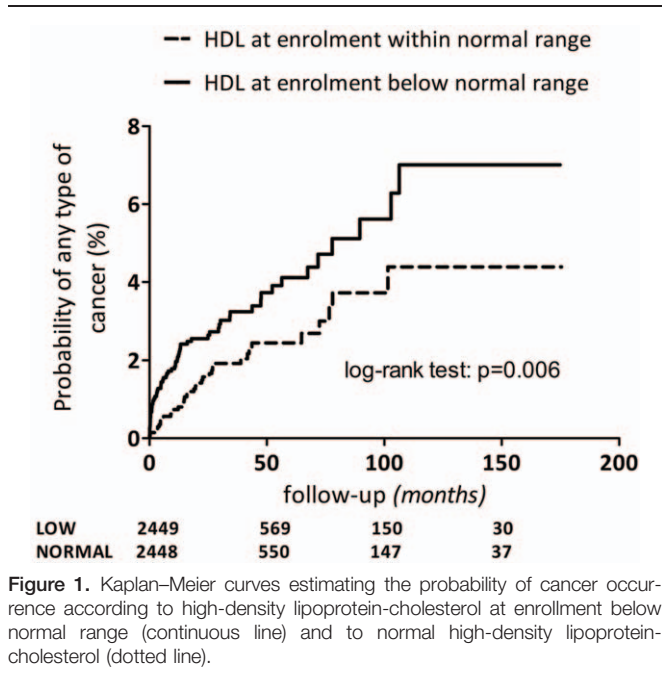


Figure 1. Kaplan-Meier curves estimating the probability of cancer occurrence according to high-density lipoprotein-cholesterol at enrollment below normal range (continuous line) and to normal high-density lipoprotein-cholesterol (dotted line).

Inflammation has been purposed as a hallmark of cancer^[20] because of activation of various types of gene mutations, chromosomal rearrangement or amplification and inactivation of tumor-suppressive genes, and of infections and inflammatory state by itself.^[21]

Apolipoprotein A1, the most important proteic component of HDL-c, *in vitro* has a direct suppressive effect on tumor cells, and *in vivo* prompts tumor-infiltrating macrophages towards tumor rejection.^[12]

Moreover, ApoA1-mimetic peptides have demonstrated anti-tumoral properties in ovarian and colon cancer experimental models *in vivo*.^[13,14]

The HDL-c and ApoA1 levels were shown to be inversely correlated with HIV-VL,^[16] and they could contribute to the documented increased prevalence of cancer in the HIV population.^[1,2]

Moreover, recent findings reported that in HIV infection, HDL-c could be dysfunctional in a model *in vitro* where HDL-c particles extracted from HIV-infected blood samples showed poorest anti-inflammatory activity on preadipocytes.^[22]

The overall cancer incidence rate in our study was almost double than that of the Italian general population,^[23,24] and it was similar to that reported in a recent study of HIV-infected patients in France and in other European countries.^[1,25–27] Among traditional risk factors for cancer that may likely explain the increase in incidence rate, our analysis first of all confirmed the role of immune depression, already reported in previous studies.^[1,28–31]

At multivariate analysis, lower CD4 nadir was a risk factor for ADM, whereas current CD4 cell count was associated with NADM, confirming the role of prior severe immune depression on ADM and suggesting a significant protective role of current CD4 in NADM. At the same time, HIV-VL was associated only with ADM, as expected. The fact that 30% of ADM occurred before ART initiation and 56% of ADM occurred during the first 6 months of follow-up, may likely explain the limited role of CD4 and ART in this subset of patients. And yet, among ADM diagnoses, there was a high proportion of KS diagnoses (64%)

that occurred also in patients with high CD4 cell count,^[24] and that may explain the lack of association between current CD4 and ADM in our study. Another potential explanation of the limited role of current CD4 in ADM occurrence is that the mean CD4 cell count increase during follow-up was not statistically significant as opposed to what occurred among subjects with a NADM diagnosis (data not shown). The prominent role of CD4 nadir as risk factor for ADM also emerged in the analysis considering only cancers that occurred after ART initiation (Table 6). The strong relationship between lower nadir CD4 cell count and increased ADM risk is well-established.^[29–32]

As for NADM, there is mounting evidence for an inverse relationship between current CD4 cell count and NADM risk,^[33–36] and almost previous studies consistently suggest that the current/latest CD4 cell count, reflecting subclinical immunodeficiency, is an important marker of short-term NADM risk (especially infection-related cancers) even in those individuals within high CD4 cell count strata more than 200 to 350/ μ L.^[37] However, nadir CD4 was also independently associated with incident NADM,^[32] and also the CD4 cell recovery, which also seemed to be an important factor for controlling the excess risk of some cancers.^[1]

Another concern is that the lack of association with ART exposure could be due to the high incidence of ADM in the first 6 months of therapy and to the small period of observation. However, we demonstrated a protective role of ART when only cancer occurrence after ART initiation was considered (Table 6).

Among NADM, Hodgkin lymphoma (21%) was the most commonly occurring cancer, followed by lung cancer (15%) and anal cancer (6%), as has been described in the literature.^[1,38] We reported 4 HCCs and no association with HCV-Ab positivity, but a significant HR at multivariate analysis associated with HBsAg positivity (HR 2.65, 95% CI 1.01–6.98) (see Table 5). Surprisingly, we found 7 diagnoses of bladder cancer, which is infrequently reported in HIV population.^[39] Human papillomavirus (HPV) colonization, predominant in HIV-infected patients,^[40] may be responsible for this increased incidence, as demonstrated in a recent meta-analysis.^[41]

In comparison with the association between low HDL-c and type of cancer in the general population, we found a different pattern of malignancy in HIV-infected patients; breast cancer, endometrial cancer, pancreatic, prostate, and colon and rectal cancer, all associated with low HDL-c in HIV-negative population,^[10,11] were poorly represented in our analysis of NADM.

It is possible that immune perturbation due to HIV infection and certain coinfections, such as HPV, HCV, hepatitis B virus (HBV), and Herpes viruses, deeply influence the prevalence of some types of cancer.

We did not find an association with smoking and cancer occurrence. This result could be due to the low incidence of cancers highly associated with smoking occurrence in our study^[42]: overall, we observed 13 cancers (12.5%) highly associated with tobacco smoking (7 lung, 1 larynx, 1 stomach, and 3 anal cancers). Most of the cancers we observed were, in fact, KS (36 cases, 34.6%), a cancer in which the role of smoking remains to be elucidated.^[43]

Our study does have some limitations. First, the number of events was rather small, given the brief follow-up. This is particularly true when results are split up into the 2 subgroups of ADM and NADM, since most of the cancer diagnoses (especially ADM) occurred within the first 12 months. We therefore cannot exclude that these diagnoses were already present at HIV

Table 3

Univariate Cox proportional-hazard models on the risk of any type of malignancy, the risk of AIDS-defining malignancies and the risk of non-AIDS-defining malignancies.

Characteristics	Any type of malignancy		ADM		NADM	
	Hazard ratio (95% confidence interval)	P	Hazard ratio (95% confidence interval)	P	Hazard ratio (95% confidence interval)	P
Age at enrollment (per 5 y older)	1.33 (1.23–1.44)	<0.001	1.23 (1.10–1.37)	<0.001	1.46 (1.29–1.64)	<0.001
Sex						
Females vs males	0.83 (0.51–1.36)	0.465	0.97 (0.51–1.84)	0.929	0.69 (0.32–1.47)	0.333
Nationality						
Non-Italian vs Italian	0.67 (0.36–1.22)	0.187	0.91 (0.45–1.87)	0.805	0.37 (0.12–1.19)	0.096
Smoke						
Yes vs no	1.11 (0.74–1.66)	0.615	0.99 (0.57–1.71)	0.973	1.27 (0.70–2.32)	0.432
Unknown vs no	1.33 (0.65–2.71)	0.436	0.93 (0.33–2.67)	0.897	1.97 (0.74–5.26)	0.178
HIV transmission risk		0.865		0.674		0.452
IDU vs MSM	1.03 (0.53–2.00)	0.922	0.61 (0.21–1.74)	0.355	1.75 (0.72–4.28)	0.218
Heterosexual vs MSM	0.93 (0.61–1.43)	0.741	0.74 (0.42–1.32)	0.310	1.26 (0.65–2.43)	0.497
Other vs MSM	1.27 (0.62–2.60)	0.514	0.87 (0.31–2.48)	0.793	1.99 (0.73–5.43)	0.180
HCV-Ab		0.825		0.333		0.183
Positive vs negative	1.14 (0.60–2.16)	0.697	0.51 (0.16–1.65)	0.262	2.12 (0.95–4.74)	0.066
Unknown vs negative	0.92 (0.59–1.42)	0.699	0.71 (0.38–1.30)	0.265	1.26 (0.67–2.36)	0.482
HBsAg		0.264		0.272		0.030
Positive vs negative	1.72 (0.75–3.95)	0.205	0.47 (0.07–3.43)	0.458	3.63 (1.40–9.42)	0.008
Unknown vs negative	0.83 (0.54–1.29)	0.413	0.62 (0.34–1.16)	0.138	1.15 (0.62–2.14)	0.650
Nadir CD4 (per 100 cells/mm ³ higher)	0.66 (0.58–0.76)	<0.001	0.54 (0.44–0.66)	<0.001	0.82 (0.69–0.97)	0.023
Calendar year of enrollment (per year longer)	0.98 (0.93–1.03)	0.487	1.03 (0.96–1.11)	0.438	0.93 (0.87–1.00)	0.055
Calendar year of first HIV positive test (per year longer)	0.99 (0.96–1.03)	0.731	1.03 (0.98–1.08)	0.299	0.97 (0.92–1.00)	0.098
ART exposure*						
Yes vs no	0.33 (0.22–0.50)	<0.001	0.21 (0.12–0.37)	<0.001	0.57 (0.31–1.06)	0.075
CD4 at enrollment (per 100 cells/mm ³ higher)	0.82 (0.75–0.89)	<0.001	0.71 (0.63–0.81)	<0.001	0.93 (0.83–1.04)	0.225
Current CD4 (per 100 cells/mm ³ higher)*	0.64 (0.58–0.71)	<0.001	0.55 (0.47–0.64)	<0.001	0.73 (0.64–0.84)	<0.001
CD4% at enrollment (per 5% higher)	0.85 (0.77–0.94)	0.001	0.79 (0.69–0.91)	0.001	0.93 (0.81–1.06)	0.280
Current CD4% (per 5% higher)*	0.69 (0.62–0.77)	<0.001	0.56 (0.48–0.66)	<0.001	0.85 (0.73–0.98)	0.030
CD8 at enrollment (per 100 cells/mm ³ higher)	0.95 (0.90–0.99)	0.027	0.96 (0.90–1.02)	0.208	0.93 (0.86–1.00)	0.057
Current CD8 (per 100 cells/mm ³ higher)*	0.96 (0.91–1.01)	0.119	0.98 (0.91–1.05)	0.587	0.94 (0.86–1.01)	0.101
CD8% at enrollment (per 5% higher)	1.01 (0.99–1.02)	0.471	1.01 (1.00–1.02)	0.119	0.98 (0.90–1.05)	0.515
Current CD8% (per 5% higher)*	1.00 (0.99–1.01)	0.619	1.00 (0.99–1.01)	0.717	1.00 (0.99–1.01)	0.737
CD4/CD8 ratio at enrollment (per point higher)	0.21 (0.08–0.51)	<0.001	0.04 (0.01–0.20)	<0.001	0.69 (0.24–1.96)	0.483
Current CD4+/CD8+ ratio (per point higher)*	0.12 (0.06–0.28)	<0.001	0.02 (0.01–0.08)	<0.001	0.37 (0.15–0.92)	0.031
HIV-RNA at enrollment (per log ₁₀ copies/mL higher)	1.21 (0.99–1.48)	0.058	1.57 (1.18–2.10)	0.002	0.93 (0.70–1.22)	0.595
Current HIV-RNA (per log ₁₀ copies/mL higher)*	1.74 (1.51–2.00)	<0.001	2.27 (1.85–2.79)	<0.001	1.29 (1.04–1.62)	0.023
Total cholesterol at enrollment (per 50 mg/dL higher)	0.99 (0.78–1.26)	0.957	0.91 (0.66–1.27)	0.592	1.09 (0.78–1.53)	0.617
Current total cholesterol (per 50 mg/dL higher)*	0.62 (0.48–0.80)	<0.001	0.49 (0.34–0.71)	<0.001	0.76 (0.54–1.08)	0.130
HDL-c at enrollment (per 10 mg/dL higher)	0.74 (0.63–0.87)	<0.001	0.81 (0.65–0.99)	0.047	0.68 (0.53–0.86)	0.002
Low vs normal	1.72 (1.16–2.56)	0.007	1.28 (0.75–2.17)	0.366	2.50 (1.35–4.76)	0.003
Current HDL-c (per 10 mg/dL higher)*	0.62 (0.53–0.74)	<0.001	0.60 (0.47–0.77)	<0.001	0.65 (0.51–0.82)	<0.001
Low vs normal*	2.84 (1.88–4.30)	<0.001	2.83 (1.57–5.09)	<0.001	2.86 (1.60–5.11)	<0.001
LDL-c at enrollment (per 50 mg/dL higher)	0.81 (0.58–1.14)	0.227	0.61 (0.38–0.99)	0.046	1.09 (0.69–1.71)	0.723
Current LDL-c (per 50 mg/dL higher)*	0.57 (0.41–0.80)	0.001	0.36 (0.21–0.60)	<0.001	0.84 (0.54–1.31)	0.448
Triglycerides at enrollment (per 50 mg/dL higher)	1.07 (1.00–1.15)	0.065	1.08 (0.97–1.19)	0.152	1.07 (0.96–1.19)	0.243
Current triglycerides (per 50 mg/dL higher)*	1.03 (0.94–1.13)	0.579	1.01 (0.88–1.16)	0.893	1.04 (0.92–1.18)	0.516

ADMs = AIDS-defining malignancies, AIDS = acquired immune deficiency syndrome, ART = antiretroviral treatment, CD4 = cluster of differentiation 4, CD8 = cluster of differentiation 8, HBsAg = hepatitis B surface antigen, HCV-Ab = hepatitis C virus-antibody, HDL-c = high-density lipoprotein-cholesterol, HIV = human immunodeficiency virus, HIV-RNA = HIV-ribonucleic acid, LDL-c = low-density lipoprotein cholesterol, nadir = lowest ever, NADMs = non-AIDS-defining malignancies.

* Time-updated variable.

infection and that they might be prevalent rather than incident events. As almost one-third of cancer diagnoses occurred within the first 3 months (43% for ADM), only 1 laboratory determination (including HDL-c) was available before cancer diagnosis: for this reason, the benefit provided by the use of time-update covariates in the analysis was fairly limited.

Additionally, our findings could be perceived to be generalized to subjects with recent HIV diagnosis, and those with regular

monitoring of HDL-c, and therefore not necessarily representative of all HIV-infected people.

In summary, our study, for the first time, reports an association between HDL-c and risk of cancer in HIV infection. HDL-c is a simple and easy marker that can be performed in every laboratory and could sort patients at higher risk for ADM and especially for NADM. Further follow-up will be needed to confirm our hypothesis.

Table 4

Multivariate Cox proportional-hazard models on the risk of any type of malignancy, the risk of AIDS-defining malignancies, and the risk of non-AIDS-defining malignancies.

Characteristics	Any type of malignancy (n=91/104)		ADM (n=44/56)		NADM (n=47/48)	
	Adjusted hazard ratio (95% confidence interval)	P	Adjusted hazard ratio (95% confidence interval)	P	Adjusted hazard ratio (95% confidence interval)	P
Age at enrollment (per 5 y older)	1.32 (1.20–1.44)	<0.001	1.16 (1.02–1.33)	0.029	1.50 (1.31–1.72)	<0.001
Sex						
Females vs males	0.94 (0.56–1.56)	0.801	1.07 (0.53–2.13)	0.859	0.79 (0.36–1.72)	0.553
Smoke		0.657		0.824		0.366
Yes vs no	1.24 (0.78–1.97)		1.08 (0.56–2.08)		1.60 (0.81–3.14)	
Unknown vs no	1.06 (0.48–2.37)		0.72 (0.21–2.48)		1.57 (0.53–4.65)	
HCV-Ab		0.954		0.400		0.637
Positive vs negative	0.94 (0.48–1.80)		0.43 (0.13–1.46)		1.49 (0.66–3.36)	
Unknown vs negative	1.10 (0.43–2.85)		0.99 (0.23–4.34)		1.18 (0.33–4.22)	
HBsAg		0.480		0.732		0.117
Positive vs negative	1.67 (0.72–3.89)		0.59 (0.08–4.36)		2.59 (0.99–6.75)	
Unknown vs negative	1.16 (0.47–2.89)		0.63 (0.14–2.74)		1.74 (0.53–5.74)	
Nadir CD4 (per 100 cells/mm ³ higher)	0.91 (0.74–1.12)	0.381	0.68 (0.50–0.92)	0.011	1.20 (0.91–1.58)	0.199
Calendar year of enrollment (per year longer)	1.10 (1.03–1.17)	0.005	1.19 (1.08–1.31)	<0.001	1.00 (0.92–1.09)	0.962
ART exposure*						
Yes vs no	1.29 (0.64–2.57)	0.477	1.32 (0.53–3.31)	0.556	1.04 (0.35–3.06)	0.944
Current CD4 (per 100 cells/mm ³ higher)*	0.78 (0.68–0.91)	<0.001	0.86 (0.70–1.06)	0.163	0.73 (0.60–0.89)	0.002
Current HIV-RNA (per log ₁₀ copies/mL higher)*	1.69 (1.36–2.11)	<0.001	2.27 (1.70–3.06)	<0.0001	1.15 (0.80–1.67)	0.448
Current HDL-c						
Low vs normal*	1.87 (1.18–2.95)	0.007	1.28 (0.66–2.49)	0.475	2.61 (1.40–4.89)	0.003
Current triglycerides (per 50 mg/dL higher)*	1.00 (0.89–1.12)	0.953	1.02 (0.86–1.21)	0.824	0.97 (0.83–1.13)	0.694

ADMs = AIDS-defining malignancies, AIDS = acquired immune deficiency syndrome, ART = antiretroviral treatment, CD4 = cluster of differentiation 4, HBsAg = hepatitis B surface antigen, HCV-Ab = hepatitis C virus-antibody, HDL-c = high-density lipoprotein-cholesterol, HIV = human immunodeficiency virus, HIV-RNA = HIV-ribonucleic acid, nadir = lowest ever, NADMs = non-AIDS-defining malignancies.

* Time-updated variable.

Table 5

Multivariate Cox proportional-hazard models on the risk of any type of malignancy, the risk of AIDS-defining malignancies, and the risk of non-AIDS-defining malignancies (including CD4/CD8 ratio).

Characteristics	Any type of malignancy (n=77/104)		ADM (n=34/56)		NADM (n=43/48)	
	Hazard ratio (95% confidence interval)	P	Hazard ratio (95% confidence interval)	P	Hazard ratio (95% confidence interval)	P
Age at enrollment (per 5 y older)	1.32 (1.19–1.46)	<0.001	1.14 (0.98–1.33)	0.087	1.49 (1.30–1.72)	<0.001
Sex						0.233
Females vs males	1.03 (0.59–1.78)	0.922	1.79 (0.84–3.82)	0.131	0.59 (0.24–1.41)	
Smoke		0.413		0.637		0.372
Yes vs no	1.39 (0.84–2.32)		1.44 (0.68–3.05)		1.57 (0.77–3.21)	
Unknown vs no	1.37 (0.60–3.15)		1.07 (0.30–3.88)		1.76 (0.59–5.26)	
HCV-Ab		0.964		0.587		0.576
Positive vs negative	1.07 (0.54–2.14)		0.53 (0.15–1.83)		1.58 (0.67–3.73)	
Unknown vs negative	1.11 (0.41–3.00)		1.12 (0.23–5.49)		1.10 (0.30–4.01)	
HBsAg		0.269		0.918		0.097
Positive vs negative	1.95 (0.83–4.60)		0.84 (0.11–6.27)		2.65 (1.01–6.98)	
Unknown vs negative	1.39 (0.53–3.63)		0.73 (0.15–3.57)		1.99 (0.59–6.75)	
Nadir CD4+ (per 100 cells/mm ³ higher)	0.91 (0.73–1.14)	0.409	0.66 (0.47–0.91)	0.013	1.19 (0.90–1.59)	0.228
Calendar year of enrollment (per year longer)	1.08 (1.01–1.15)	0.034	1.19 (1.07–1.33)	0.002	0.98 (0.90–1.07)	0.702
ART exposure*						
Yes vs no	1.16 (0.54–2.48)	0.699	1.05 (0.37–3.00)	0.933	1.11 (0.36–3.41)	0.861
Current CD4+ (per 100 cells/mm ³ higher)*	0.82 (0.70–0.97)	0.019	1.03 (0.81–1.31)	0.819	0.73 (0.59–0.90)	0.004
Current CD4/CD8 ratio (per point higher)*	0.96 (0.81–1.13)	0.594	0.77 (0.55–1.09)	0.137	1.01 (0.91–1.13)	0.823
Current HIV-RNA (per log ₁₀ copies/mL higher)*	1.62 (1.27–2.08)	<0.001	2.15 (1.52–3.03)	<0.0001	1.17 (0.80–1.73)	0.425
Current HDL-c						
Low vs normal*	1.87 (1.14–3.06)	0.013	1.19 (0.56–2.52)	0.648	2.65 (1.38–5.08)	0.003
Current triglycerides (per 50 mg/dL higher)*	1.00 (0.88–1.12)	0.943	1.08 (0.92–1.26)	0.366	0.93 (0.77–1.11)	0.397

ADMs = AIDS-defining malignancies, AIDS = acquired immune deficiency syndrome, ART = antiretroviral treatment, CD4 = cluster of differentiation 4, CD8 = cluster of differentiation 8, HBsAg = hepatitis B surface antigen, HCV-Ab = hepatitis C virus-antibody, HDL-c = high-density lipoprotein-cholesterol, HIV = human immunodeficiency virus, HIV-RNA = HIV-ribonucleic acid, nadir = lowest ever, NADMs = non-AIDS-defining malignancies.

* Time-updated variable.

Table 6

Multivariate Cox proportional-hazard models on the risk of any type of malignancy, the risk of AIDS-defining malignancies, and the risk of non-AIDS-defining malignancies in subjects exposed to antiretroviral treatment.

Characteristics	Any type of malignancy (n=71/83)		ADM (n=32/41)		NADM (n=39/42)	
	Adjusted hazard ratio (95% confidence interval)	P-value	Adjusted hazard ratio (95% confidence interval)	P	Adjusted hazard ratio (95% confidence interval)	P
Age at enrollment (per 5 y older)	1.42 (1.28–1.58)	<0.001	1.24 (1.06–1.45)	0.007	1.61 (1.38–1.87)	<0.001
Sex		0.713		0.476		0.896
Females vs males	1.12 (0.62–2.00)		1.35 (0.59–3.09)		0.95 (0.41–2.20)	
Smoke		0.405		0.980		0.299
Yes vs no	1.43 (0.84–2.42)		1.04 (0.48–2.27)		1.78 (0.86–3.68)	
Unknown vs no	1.09 (0.45–2.63)		0.90 (0.24–3.34)		1.27 (0.38–4.26)	
HCV-Ab		0.947		0.694		0.921
Positive vs negative	0.89 (0.43–1.85)		0.64 (0.18–2.25)		1.15 (0.46–2.89)	
Unknown vs negative	1.04 (0.33–3.30)		1.51 (0.24–9.32)		0.83 (0.18–3.85)	
HBsAg		0.233		0.854		0.154
Positive vs negative	2.44 (0.86–6.90)		1.25 (0.17–9.52)		3.00 (0.87–10.32)	
Unknown vs negative	1.31 (0.43–3.95)		0.64 (0.11–3.85)		2.10 (0.50–8.90)	
Nadir CD4+ (per 100 cells/mm ³ higher)		<0.001		<0.001		0.047
0.59 (0.47–0.75)			0.46 (0.33–0.64)		0.75 (0.53–0.98)	
Calendar year of enrollment (per more recent year)		0.048		0.836		0.002
0.94 (0.88–0.99)			1.01 (0.92–1.11)		0.88 (0.81–0.95)	
Months of ART (per mo longer)	0.94 (0.93–0.95)	<0.001	0.94 (0.92–0.95)	<0.001	0.94 (0.93–0.96)	<0.001
Current CD4 (per 100 cells/mm ³ higher)*		0.540		0.730		0.302
0.96 (0.83–1.10)			1.03 (0.86–1.25)		0.90 (0.73–1.10)	
Current HIV-RNA (per log ₁₀ copies/mL higher)*		0.316		0.002		0.113
1.10 (0.91–1.33)			1.51 (1.16–1.96)		0.78 (0.58–1.06)	
Current HDL-c		<0.001		0.221		0.001
Low vs normal*	2.39 (1.44–3.96)		1.62 (0.75–3.48)		3.14 (1.59–6.21)	
Current triglycerides (per 50 mg/dL higher)*		0.709		0.750		0.529
0.98 (0.86–1.11)			1.03 (0.85–1.25)		0.94 (0.79–1.13)	

ADMs = AIDS-defining malignancies, AIDS = acquired immune deficiency syndrome, ART = antiretroviral treatment, CD4 = cluster of differentiation 4, HBsAg = hepatitis B surface antigen, HCV-Ab = hepatitis C virus-antibody, HDL-c = high-density lipoprotein-cholesterol, HIV = human immunodeficiency virus, HIV-RNA = HIV-ribonucleic acid, nadir = lowest ever, NADMs = non-AIDS-defining malignancies.

*Time-updated variable.

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References

- [1] Hleyhel M, Hleyhel M, Bouvier AM, et al. Risk of non-AIDS-defining cancers among HIV-1-infected individuals in France between 1997 and 2009: results from a French cohort. *AIDS* 2014;28:2109–18.
- [2] Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative incidence of cancer among persons with HIV in North America: a cohort study. *Ann Intern Med* 2015;163:507–18.
- [3] Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;420:860–7.
- [4] Neuhaus J, Jacobs DR Jr, Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *J Infect Dis* 2010;201:1788–95.
- [5] Younas M, Psomas C, Reynes J, et al. Immune activation in the course of HIV-1 infection: Causes, phenotypes and persistence under therapy. *HIV Med* 2016;17:89–105.

- [6] Khovidhunkit W, Memon RA, Feingold KR, et al. Infection and inflammation-induced proatherogenic changes of lipoproteins. *J Infect Dis* 2000;181(suppl 3):S462–72.
- [7] de la Llera Moya M, McGillicuddy FC, Hinkle CC, et al. Inflammation modulates human HDL composition and function in vivo. *Atherosclerosis* 2012;222:390–4.
- [8] Yamagishi S, Adachi H, Matsui T, et al. Decreased high-density lipoprotein cholesterol level is an independent correlate of circulating tumor necrosis factor- α in a general population. *Clin Cardiol* 2009;32:E29–32.
- [9] Sarov-Blat L, Kiss RS, Haidar B, et al. Predominance of a proinflammatory phenotype in monocyte-derived macrophages from subjects with low plasma HDL-cholesterol. *Arterioscler Thromb Vasc Biol* 2007;27:1115–22.
- [10] Melvin JC, Holmberg L, Rohrmann S, et al. Serum lipid profiles and cancer risk in the context of obesity: four meta-analyses. *J Cancer Epidemiol* 2013;2013:823849.
- [11] Jafri H, Alsheikh-Ali AA, Karas RH. Baseline and on-treatment high-density lipoprotein cholesterol and the risk of cancer in randomized controlled trials of lipid-altering therapy. *J Am Coll Cardiol* 2010;55:2846–54.
- [12] Zamanian-Daryoush M, Lindner D, Tallant TC, et al. The cardioprotective protein apolipoprotein A1 promotes potent anti-tumorigenic effects. *J Biol Chem* 2013;288:21237–52.
- [13] Su F, Grijalva V, Navab K, et al. HDL mimetics inhibit tumor development in both induced and spontaneous mouse models of colon cancer. *Mol Cancer Ther* 2012;11:1311–9.
- [14] Su F, Kozak KR, Imaizumi S, et al. Apolipoprotein A-I (apoA-I) and apoA-I mimetic peptides inhibit tumor development in a mouse model of ovarian cancer. *Proc Natl Acad Sci U S A* 2010;107:19997–20002.
- [15] Mujawar Z, Rose H, Morrow MP, et al. Human immunodeficiency virus impairs reverse cholesterol transport from macrophages. *PLoS Biol* 2006;4:e365.
- [16] Baker JV, Neuhaus J, Duprez D, et al. Inflammation predicts changes in high-density lipoprotein particles and apolipoprotein A1 following initiation of antiretroviral therapy. *AIDS* 2011;25:2133–42.
- [17] d'Arminio Monforte A, Lepri AC, Rezza G, et al. Italian Cohort of Antiretroviral-Naive Patients: Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.C.O.N.A. Study Group. *AIDS* 2000;14:499–507.
- [18] Mussini C, Lorenzini P, Cozzi-Lepri A, et al. CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: an observational cohort study. *Lancet HIV* 2015;2:e98–106.
- [19] Murphy AJ, Woollard KJ, Hoang A, et al. High-density lipoprotein reduces the human monocyte inflammatory response. *Arterioscler Thromb Vasc Biol* 2008;28:2071–7.
- [20] Colotta F, Allavena P, Sica A, et al. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009;30:1073–81.
- [21] Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. *Nature* 2008;454:436–44.
- [22] Njoroge A, Yeop Han C, Chait A, et al. Dysfunctional HDL among HIV-infected adults in Nairobi: a pilot study. (abstract WEPEB351) in abstract book of the 8th International AIDS Society (IAS) conference on HIV pathogenesis, treatment & prevention; 2015; 19–22 July 2015, Vancouver, Canada.
- [23] Available from: <http://itacan.ispo.toscana.it/English/StatsFact.asp?cancer=450&country=39000>. Accessed July 3, 2016.
- [24] Calabresi A, Ferraresi A, Festa A, et al. Incidence of AIDS-defining cancers and virus-related and non-virus-related non-AIDS-defining cancers among HIV-infected patients compared with the general population in a large health district of Northern Italy, 1999–2009. *HIV Med* 2013;14:481–90.
- [25] Hleyhel M, Belor A, Bouvier AM, et al. Risk of AIDS-defining cancers among HIV-1-infected patients in France between 1992 and 2009: results from the FHDH-ANRS CO4 cohort. *Clin Infect Dis* 2013;57:1638–47.
- [26] Dauby N, De Wit S, Delforge M, et al. Characteristics of non-AIDS-defining malignancies in the HAART era: a clinico-epidemiological study. *J Int AIDS Soc* 2011;14:16.
- [27] Martinez E, Milinkovic A, Buira E, et al. Incidence and causes of death in HIV-infected persons receiving highly active antiretroviral therapy compared with estimates for the general population of similar age and from the same geographical area. *HIV Med* 2007;8:251–8.
- [28] Hessol NA, Martinez-Maza O, Levine AM, et al. Lung cancer incidence and survival among HIV-infected and uninfected women and men. *AIDS* 2015;29:1183–93.
- [29] Richel O, Van Der Zee RP, Smit C, et al. Brief report: anal cancer in the HIV-positive population: slowly declining incidence after a decade of cART. *J Acquir Immune Defic Syndr* 2015;69:602–5.
- [30] Clifford GM, Franceschi S, Keiser O, et al. Immunodeficiency and the risk of cervical intraepithelial neoplasia 2/3 and cervical cancer: a nested case-control study in the Swiss HIV cohort study. *Int J Cancer* 2016;138:1732–40.
- [31] Dubrow R, Silverberg MJ, Park LS, et al. HIV infection, aging, and immune function: implications for cancer risk and prevention. *Curr Opin Oncol* 2012;24:506–16.
- [32] Patel P, Armon C, Chmiel JS, et al. Factors associated with cancer incidence and with all-cause mortality after cancer diagnosis among human immunodeficiency virus-infected persons during the combination antiretroviral therapy era. *Open Forum Infect Dis* 2014;1:ofu012.
- [33] Borges AH, Dubrow R, Silverberg MJ. Factors contributing to risk for cancer among HIV-infected individuals, and evidence that earlier combination antiretroviral therapy will alter this risk. *Curr Opin HIV AIDS* 2014;9:34–40.
- [34] Petoumenos K, van Leuwen MT, Vajdic CM, et al. Cancer, immunodeficiency and antiretroviral treatment: results from the Australian HIV Observational Database (AHOD). *HIV Med* 2013;14:77–84.
- [35] Prosperi MC, Cozzi-Lepri A, Castagna A, et al. Incidence of malignancies in HIV-infected patients and prognostic role of current CD4 cell count: evidence from a large Italian cohort study. *Clin Infect Dis* 2010;50:1316–21.
- [36] Reekie J, Kosa C, Engsig F, et al. Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies. *Cancer* 2010;116:5306–15.
- [37] Achhra AC, Petoumenos K, Law MG. Relationship between CD4 cell count and serious long-term complications among HIV-positive individuals. *Curr Opin HIV AIDS* 2014;9:63–71.
- [38] Engels EA. Non-AIDS-defining malignancies in HIV-infected persons: etiologic puzzles, epidemiologic perils, prevention opportunities. *AIDS* 2009;23:875–85.
- [39] Chawki S, Ploussard G, Montlahuc C, et al. Bladder cancer in HIV-infected adults: an emerging concern? *J Int AIDS Soc* 2014;17(4 suppl 3):19647.
- [40] Geskus RB, Gonzalez C, Torres M, et al. Incidence and clearance of anal high-risk human papillomavirus in HIV-positive men who have sex with men: estimates and risk factors. *AIDS* 2016;30:37–44.
- [41] Li N, Yang L, Zhang Y, et al. Human papillomavirus infection and bladder cancer risk: a meta-analysis. *J Infect Dis* 2011;204:217–23.
- [42] Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. *Int J Cancer* 2008;122:155–64.
- [43] Luu HN, Amirian ES, Scheurer ME. The interaction between smoking status and highly active antiretroviral therapy (HAART) use on the risk of Kaposi's sarcoma (KS) in a cohort of HIV-infected men. *Br J Cancer* 2013;108:1173–7.