Elevated triglycerides and risk of MI in HIV-positive persons, the D:A:D study

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Objectives: The purpose of this analysis was to explore the relationship between elevated TG levels and the risk of MI in HIV-positive persons, after adjustment for total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C) and non-lipid risk factors

Background: Although elevated triglyceride (TG) levels are commonly noted in HIV-positive individuals, it is unclear whether they represent an independent risk factor for myocardial infarction (MI).

Methods: The incidence of MI during follow-up was stratified according to the latest TG level. Multivariable Poisson regression models were used to describe the independent association between the latest TG level and MI risk after adjusting for TC and HDL-C, non-lipids cardiovascular disease (CVD) risk factors, HIV and treatment related factors.

Results: The 33,308 persons included in the study from 1999–2008 experienced 580 MIs over 178,835 person-years. Unadjusted, the risk of MI increased by 67% (relative risk [RR] 1.67 [95% confidence interval 1.54–1.80]) per doubling in TG level. After adjustment for the latest TC and HDL-C level, the RR dropped to 1.33 [1.21, 1.45]; this effect was further attenuated by other CVD risk factors, the RR was reduced to 1.17 [1.06–1.29]. In models that additionally adjusted for HIV and treatment factors, the risk was further diminished, although remained significant (1.11 [1.01–1.23]).

Conclusions: Higher TG levels were marginally independently associated with an increased risk of MI in HIV-positive persons, although the extent of the reduction in relative risk after taking account of latest TC, latest HDL-C and other confounders, suggests that any independent effect is small.

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Introduction:

Elevated triglyceride (TG) levels are common in HIV-positive persons for several reasons. Firstly, conditions that traditionally result in elevated TG, such as insulin resistance, diabetes mellitus (DM) and fatty liver are prevalent in the HIV-positive population [1–4]. Secondly, the physiological distress that results from untreated HIV infection may cause lipid perturbations, in particular elevated TG [5,6]. Indeed, it has been suggested that HIV-positive patients may experience increased post-prandial TG levels[7], this being one potential explanation for the increased risk of myocardial infarction (MI) that is seen in HIV-positive persons. The presence of increased levels of atherogenic remnant lipoproteins (chylomicron remnants and very low-density lipoprotein remnants) might be associated with increased levels of nonfasting triglycerides. These smaller triglyceride-rich lipoproteins may penetrate the endothelial cell layer where they can contribute to the formation of foam cells, involved in early stages of atherosclerosis [8].

Finally, elevated TG is a frequent side-effect of antiretroviral therapy [9–11]. Different antiretroviral drugs have different propensities to cause elevated TG, with drugs from the protease inhibitor (PI) class, but also the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz and some nucleoside reverse transcriptase inhibitor (NRTI) drugs [9–11] all being reported to cause elevated TG. Some of these drugs have been associated with an increased risk of MI in HIV-positive patients [12,13].

The extent to which elevated TG is a cause of or even an independent risk factor for CVD in the general population remains controversial. Some recent papers have identified elevated TG as an independent risk factor for CVD after adjusting for high density- lipoprotein (HDL-C) and total cholesterol (TC) [14,15]. However a recent meta-analysis concluded that there was no independent effect of elevated TG on the risk of MI [16]. In HIV-positive persons, where the causes and clinical implications of elevated TG may differ, it is particularly unclear whether TG levels provide additional prognostic information regarding MI risk once TC and HDL-C are taken into account. The purpose of this analysis is therefore to explore the independent relationship between elevated TG levels and the risk of MI in HIV-positive persons, after adjustment for cardiovascular risk factors (including TC and HDL-C), HIV and treatment related factors.

Methods

The D:A:D study is a prospective, observational study formed by the collaboration of 11 cohorts following HIV-positive subjects from 212 clinics in Europe, Australia and the US. The primary objective of the study is to investigate the possible association between combination antiretroviral therapy (cART) and the onset of MI. The D:A:D study methodology has been described in detail [12].

Data collection

Patients are followed prospectively during visits to outpatient clinics as a part of regular medical care. At enrolment and at least every 8 months thereafter standardized data collection forms are completed at the sites providing information concerning family history of coronary heart disease, prior history of CVD and DM, cigarette smoking, blood pressure, lipid-lowering and anti-hypertensive therapy, the presence of physician documented lipodystrophy and serum lipid levels (TC, HDL-C, TG levels and information on fasting conditions), as well as HIV-related information (antiretroviral therapy, CD4 cell counts, HIV viral loads and dates of diagnoses of all AIDS-defining diseases).

End-points

All incident cases of MI are reported to the study coordinating office for validation and coding Reported MIs are classified as definite, possible, or unclassifiable, according to criteria applied in the WHO MONICA study independently of knowledge of a patient's antiretroviral treatment history (with cardiologist input). Patients who had already experienced an MI, or coronary revascularisation (bypass or angioplasty) or a stroke prior to study entry were defined as having previous CVD. These events were not validated centrally. Only the first MI during prospective follow-up was included in the present analysis.

Statistics

Follow-up was counted from D:A:D enrolment until the first MI event, the date of death, 1st February 2008 or 6 months after the patient's last clinic visit (whichever occurred first). Each patient's follow-up period was split into a series of consecutive one-month periods, and his/her covariate data was updated (if this information had changed) at the start of each month. For the purpose of this analysis, fasting status of the lipids was not taken into consideration ie. there was no requirement for triglycerides to be performed in a fasting or non-fasting state.

As an exploratory analysis, the incidence of the first MI during prospective D:A:D follow-up was calculated according to the latest (time-updated) TG, TC and HDL-C level. For the purposes of these analyses, the latest measurement of each lipid was stratified into quintiles based on the distribution of levels across all measures on all people (see Table 2 for categories), with an additional category for follow-up and events in patients in whom no measurement was available. As these analyses were time-updated, person-years of follow-up and any events that

occur will be allocated to the most recently available TG measurement at the time; if a new TG measurement becomes available, then subsequent person-years and events are allocated to the new value. This information was used to assess the appropriateness of incorporating each measurement into a regression model as a continuous covariate.

Using Poisson regression we analysed the relationships between the development of MI and each lipid measurement separately, followed by each pair of measurements, then all three lipids adjusted for one another in the same model. Based on the exploratory analyses, the latest TG and TC levels were incorporated into these models as continuous time-updated covariates (with the TG level being $\log_2$ transformed prior to inclusion, thus estimates are per doubling in TG level), whereas the HDL-C level was incorporated as a categorical time-updated covariate (due to the higher proportion of follow-up time without a measurement available) with six levels, including category for missing HDL-C. We then repeated these analyses after adjusting for other CVD risk factors (age (continuous covariate), sex, ethnicity, mode of infection, body mass index (BMI), smoking status, previous CVD event (CVD events before and after baseline, excluding MI after baseline), family history of CVD and calendar year (all categorical covariates)). All analyses were performed using the GENMOD procedure in SAS.

Several further adjusted analyses were performed. Firstly, we re-ran the model after additionally adjusting for the latest $CD4^+$ cell count and HIV RNA level (both fitted as time-updated covariates) as well as cumulative exposure to the PI, NRTI and NNRTI drug classes. Secondly, as DM and the use of lipid-lowering drugs may both have an impact on MI risk and may also occur more frequently in those receiving antiretroviral therapy, we included adjustment for these in our model, again as time-updated covariates thus reflecting the changing status of an individual over time. We next additionally adjusted for blood glucose level, another factor that may lie on the causal pathway between antiretroviral treatment and MI risk. Given the high proportion of follow-up time where no HDL-C measurement was available, we then repeated our main analyses after using multiple imputation methods to complete the missing lipid data. Specifically, we used PROC MI in SAS to impute missing lipid measurements (TG, TC and HDL) at baseline. Variables included in the model used to impute baseline lipids were baseline covariates (age, sex, ethnicity, risk group, BMI, smoking status and prior CVD) and whether the patient developed an MI over follow-up; imputed values were then carried forward until the time of the first available measurement for each individual. Five datasets were imputed and the MI procedure in SAS was used to combine the relative rate estimates from the five different datasets. To explore whether any apparent relationship between the latest TG level and MI risk was being driven by a small number of individuals with particularly high TG levels, we further stratified the highest TG group into 3–4 mmol/L, 4–5 mmol/L and >5 mmol/L. Finally, as several drugs have been reported to be associated with an increased TG level, most notably lopinavir/r and ritonavir, we investigated whether there was a statistical interaction between the latest TG level and ever or current receipt of these drugs. Such an interaction might indicate a different clinical relevance of raised TG levels in patients receiving these drugs to those in patients not receiving them.

Results

The 33,308 patients included in the D:A:D Study were followed for a total of 178,835 person-years (PY, median 5.8 [IQR 3.9, 7.5] per person) over which time 580 incident MIs occurred (event rate 3.2/1000 PY, 95% confidence interval [3.0, 3.5]). Overall 30703 (92.2%) patients had a least one TG measurement available; these patients contributed 435,658 TG measurements to the analysis (median 13, interquartile range [7,18] per person). Of these, 25.7% were known to be measured in a fasting state and 12.1% in a non-fasting state; information on fasting state was not available for the remaining 62.2% of TG measures. Overall, the median (interquartile range) TG measurement was 1.70 (1.10, 2.80) mmol/L (n = 435,658), the median TC measurement was 5.00 (4.20, 5.90) mmol/L (n = 425,677) and the median HDL-C measurement was 1.18 (0.94, 1.45) mmol/L (n = 303,075).

Most of the patients included in the analysis were male (74.1%), white (53.6%) and likely mode of HIV acquisition was through sex between men (43.2%). Around a third (34.7%) of patients were current smokers, 2.9% had DM, and 18.8% were co-infected with hepatitis C (Table 1). A total of 3.1% had a BMI < 18 kg/m^2, 4.5% had a BMI >30 kg/m^2, and 4.1% were on a lipid lowering drug. Their median latest CD4 count was 408 (IQR 249–600) cells/mm^3 and 32% of patients were virologically suppressed (≤50 copies/ml), of which 97.8% were antiretroviral therapy (ART) experienced.

Risk of MI associated with elevated TG levels

The incidence of MI increased as TG levels increased, from 1.1/1000 PY in those with TG<1.00 mmol/L to 6.1/1000 PY in those with TG>3.00 mmol/L (Table 2). Similarly, the incidence of MI increased as TC increased, from 1.8/1000 PY in those with TC<4.0 mmol/L to 6.7/1000 PY in those with TC>6.1 mmol/L. In contrast, the incidence of MI decreased as HDL-C levels increased, from 4.4/1000 PY in those with HDL-C<0.90 mmol/L to 1.9/1000 PY in those with HDL-C>1.60 mmol/L.

Table 1. Characteristics of patients entry in the D:A:D study.

Number of patients (percentage)	33 308 (100)
Male sex	24 669 (74.1)
Race	
White	17 835 (53.6)
Black	3 548 (10.7)
Other	1 051 (3.2)
Unknown	10 874 (32.7)
BMI kg/m^2	
<18	1 038 (3.1)
18 – 26	22 073 (66.3)
26 – 30	4 237 (12.7)
>30	1 504 (4.5)
Unknown	4 456 (13.4)
Mode of infection	
Sex between men	14 388 (43.2)
Sex between men and women	10 017 (30.1)
Injection drug use	5 997 (18.0)
Other/unknown	2 906 (8.7)
Smoking Status	
Current smoker	11 572 (34.7)
Ex-smoker	6 120 (18.4)
Never smoked	9 014 (27.1)
Unknown	6 602 (19.8)
Family history of CVD	
Yes	2 312 (6.9)
No	22 631 (67.9)
Unknown	8 365 (25.1)
Previous CVD[a]	
Yes	537 (1.6)
No	32 771 (98.4)
Diabetes Mellitus	
Yes	976 (2.9)
No	32 322 (97.1)
Receipt of lipid lowering drugs	
Yes	1 357 (4.1)
No	21 922 (65.8)
Unknown	10 029 (30.1)
Co-infected with hepatitis C virus	
Yes	6 257 (18.8)
No	17 520 (52.6)
Unknown	9 531 (28.6)
Previous exposure to ART	
PIs	19 355 (58.1)
NNRTIs	11 112 (33.4)
NRTIs	24 308 (73.0)
Median value (IQR); number of patients	
Age (years)	39 (34 – 45); 33307
BMI (kg/m^2)	23 (21 – 25); 28852
Log HIV-1 RNA (copies/ml)	2.7 (1.7 – 4.2); 32085
CD4 counts (cells/mm^3)	408 (249 – 600); 32442
Lipids	
HDL cholesterol	1.1 (0.9 – 1.4); 15 123
Total cholesterol	4.9 (4.1 – 5.9); 27656
Triglycerides	1.6 (1.0 – 2.6); 27646

[a]Patients who had already experienced an MI, or coronary revascularisation (bypass or angioplasty) or a stroke prior to study entry.

Results from unadjusted analyses of the association between TG level and MI mirrored the crude analyses described above. In particular, in unadjusted analyses, each doubling in the latest TG level was associated with a 67% increased risk of MI (relative rate (RR) 1.67, [95% confidence interval 1.54, 1.80], Table 3, model 1). We next considered the impact of adjusting for the other lipid markers on the association between TG and MI, but without adjusting for any other potential confounder. After adjusting for the latest HDL-C level (model 5), the RR associated with a doubling of TG level did not change appreciably (RR 1.63 [1.50, 1.77]), but adjustment for the latest TC measurement (model 4) did lead to a reduction in the RR associated with an elevated TG (RR 1.43 [1.32, 1.56]). Adjustment for both the latest TC *and* HDL-C measurement (model 7) reduced the association further (1.33 [1.21, 1.45]). Of note, the latest TC and HDL-C measurements remained strongly associated with MI risk in all models (Table 3).

Figure 1 shows the association between the latest TG level and MI risk after adjusting for the latest TC and HDL-C levels as well as the results from additional adjusted analyses. Further adjustment for other CVD risk factors, as well as for HIV and treatment related factors, reduced the association between a doubling of TG and MI risk further, from 1.33 to 1.17 and 1.11 respectively. At this point, further adjustment for DM and the use of lipid-lowering drugs, as well as for blood glucose levels, had no additional impact on the RR associated with elevated TG, although confidence intervals were widened slightly.

In models that used multiple imputation methods to impute lipid data, the association between a doubling of TG and MI risk (after adjustment for other lipids as well as CVD risk factors) changed from 1.17 [1.05, 1.30] to 1.18 [1.07, 1.30]. To exclude the possibility that the apparent residual association between a doubling of TG and an increased risk of MI was being driven by a small number of patients with very high levels of TG, we repeated the analyses after subdividing the highest TG strata further. The results were unchanged, and continued to support a gradual increase in MI risk as the TG level increased (data not shown). Although sensitivity analyses suggested that the association between raised TG levels and MI risk might be slightly stronger in women (1.14 [0.79, 1.64]) than in men (1.10 [0.99, 1.23]), a formal interaction test was non-significant ($p = 0.20$). Whilst the test of interaction between older age (≥40 years) and raised TG levels was significant ($p = 0.01$), estimates in the two age groups did not differ greatly (<40 years: 1.15 [0.86, 1.52]; ≥40 years: 1.11 [1.00, 1.24]). Finally, we explored if the 'residual effect' of TG of 11% was explained by ART-induced TG changes. But there was no such evidence or modification by exploring an interaction with drugs and TG.

Discussion

Despite the fact the elevated TG is a frequent side effect of antiretroviral therapy, the association between elevated TG and the risk of MI has never yet been assessed in a study with clinical end-points. In the present study, we found that higher TG levels were independently associated with an increased risk of MI. However, the residual effect of elevated TG levels after adjustment for

Table 2. Myocardial infarction event rates (per 1000 person-years) according to the latest measurement of TG, TC and HDL-C.

	Number of myocardial infarctions	Person-years	Event rate (/1000 person-years)	95% confidence interval
TG (mmol/L)				
<1.0	38	33765	1.1	0.8, 1.5
1.0–1.4	80	35942	2.2	1.7, 2.7
1.4–2.0	95	31753	3.0	2.4, 3.6
2.0–3.0	136	32623	4.2	3.5, 4.9
≥3.0	206	33984	6.1	5.2, 6.9
Missing	25	10768	2.3	1.4, 3.2
TC (mmol/L)				
<4.0	56	30943	1.8	1.3, 2.3
4.0–4.7	69	37925	1.8	1.4, 2.2
4.7–5.3	82	33019	2.5	1.9, 3.0
5.3–6.1	131	34094	3.8	3.2, 4.5
>6.1	219	32845	6.7	5.8, 7.6
Missing	23	10010	2.3	1.4, 3.2
HDL-C (mmol/L)				
<0.9	123	28194	4.4	3.6, 5.1
0.9–1.1	124	28791	4.3	3.5, 5.1
1.1–1.3	99	26461	3.7	3.0, 4.5
1.3–1.6	82	26142	3.1	2.5, 3.8
≥1.6	42	22146	1.9	1.3, 2.5
Missing	110	47102	2.3	1.9, 2.8

TC, HDL-C and non-lipid risk factors was very small (11% per doubling in TG) compared with the original unadjusted effect size of 67%. Overall these findings suggests that MI risk stratification in HIV-positive subjects should focus more on other modifiable risk factors than elevated TG.

Table 3. Relationships between the development of myocardial infarction and the latest measurement of each lipid.

Model number	Lipids		Relative rate	95% confidence interval	p value
Separate models for each lipid					
1	TG	per $\log_2$ higher	1.67	1.54, 1.80	<0.001
2	TC	per mmol/L higher	1.29	1.26, 1.33	<0.001
3	HDL-C	<0.9	2.30	1.62, 3.26	<0.001
		0.9–1.1	2.27	1.60, 3.22	
		1.1–1.3	1.97	1.38, 2.83	
		1.3–1.6	1.65	1.14, 2.40	
		≥1.6	1	–	
		Missing	1.23	0.86, 1.76	
Models for each pair of lipid measurements					
4	TG	per $\log_2$ higher	1.43	1.32, 1.56	<0.001
	TC	per mmol/L higher	1.23	1.17, 1.28	<0.001
5	TG	per $\log_2$ higher	1.63	1.50, 1.77	<0.001
	HDL-C	<0.9	1.36	0.94, 1.95	0.005
		0.9–1.1	1.52	1.07, 2.18	
		1.1–1.3	1.47	1.02, 2.11	
		1.3–1.6	1.41	0.97, 2.05	
		≥1.6	1	–	
		Missing	0.96	0.66, 1.39	
6	TC	per mmol/L higher	1.32	1.28, 1.36	<0.001
	HDL-C	<0.9	3.04	2.12, 4.36	<0.001
		0.9–1.1	2.75	1.92, 3.94	
		1.1–1.3	2.29	1.58, 3.31	
		1.3–1.6	1.88	1.29, 2.75	
		≥1.6	1	–	
		Missing	1.53	1.05, 2.23	
Model including all three lipid measurements					
7	TG	per $\log_2$ higher	1.33	1.21, 1.45	<0.001
	TC	per mmol/L higher	1.26	1.20, 1.32	<0.001
	HDL-C	<0.9	2.02	1.39, 2.95	<0.001
		0.9–1.1	2	1.38, 2.88	
		1.1–1.3	1.76	1.22, 2.55	
		1.3–1.6	1.59	1.09, 2.32	
		≥1.6	1	–	
		Missing	1.21	0.83, 1.77	

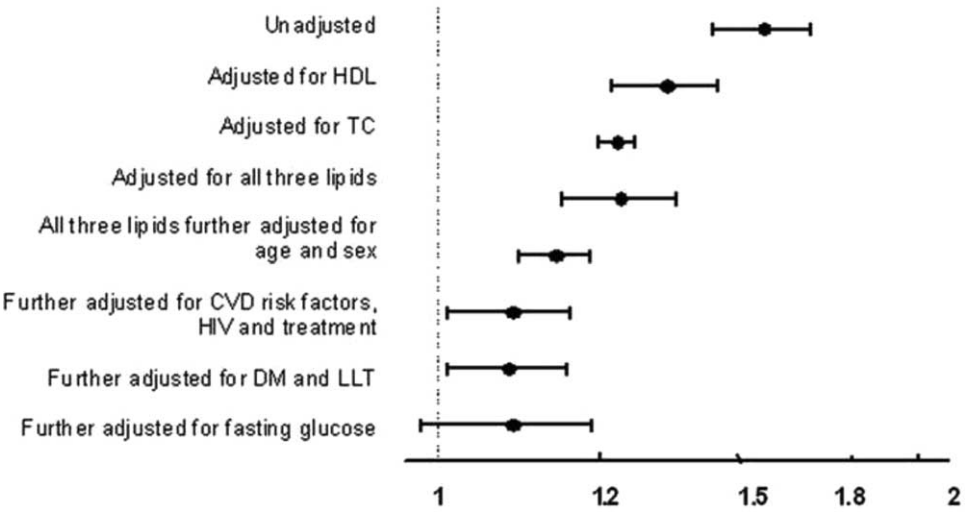

Fig. 1. Relative rate of MI per doubling (log $_2$ increase) in TG, additional adjustments. CVD risk factors: Age, sex, ethnicity, mode of infection, body mass index, smoking status, previous CVD event, family history of CVD event and calendar year. HIV factors: CD4 count and HIV RNA levels. Treatment factors: Cumulative exposure to PI, NRTI and NNRTI drug classes. DM, Diabetes mellitus; LLT, Lipidlowering therapy.

Our findings are in accordance with two recent meta-analyses based on studies conducted in the general population [16,17], where adjustment for HDL-C led to a reduction in the RR associated with TG levels from 1.37 [1.31–1.42] to 0.99 [0.94–1.05] [15], but are less concordant with findings from other studies [14,15,18–21]. One explanation for the differences between the studies may be the different CVD risk profile of the included patients: not only were patients in the D:A:D Study 10–15 years younger, on average, than subjects in most studies from the general population, but the average BMI at baseline is also much lower (median 23 kg/m^2, with 4.5% of patients having a BMI of >30 kg/m^2).

Of interest, neither the association between TC and MI risk, nor that between HDL-C and MI risk changed dramatically after adjustment for other CVD or HIV-related risk factors, and both remained significant after adjustment in multivariable models. The strong and independent association between elevated TC and MI risk has also been shown in the general population [16,17,22].

It may be anticipated that drug-induced TG changes might have a different impact on MI risk than 'lifestyle'-induced TG changes. However, a sensitivity analysis in which we explored the interaction between TG levels and use of lopinavir/r and/or ritonavir (PI drugs that are both known to lead to a rapid increase in TG levels after initiation) did not indicate that this was the case.

Although our findings are based on observational cohort data, a risk of 11% of MI associated with a doubling in TG levels would question if the use of drugs to lower TG levels (e.g. fibrates, nicotinic acid) would have a major impact on the incidence of MI in HIV-positive patients, particularly if these drugs have no other independent effects on MI risk. Two randomized controlled trials have demonstrated the effectiveness of fibrates in terms of lipid parameters in HIV-positive persons [23,24]. However no randomized controlled trial of the effect of these drugs on the risk of MI have been conducted in HIV-positive persons. Recent guidelines from the European AIDS Clinical Society (EACS) does not recommend the use of niacin and fibrates to treat elevated TG [25]

Limitations

Several limitations of our study should be noted. Firstly, information on fasting conditions was not available for all lipid measurements. Previous analysis from our study suggest that whilst the absolute level of TG measurements differed according to whether the measurement was taken in a fasting or non-fasting condition, the association between elevated TG and MI risk did not differ (D Kamara, manuscript in press). Secondly, the lack of repeated sampling and the within-person variability of TG levels may introduce bias when assessing the association with CVD, a phenomena known as regression dilution bias [26]. Whilst this is unlikely to have a major impact on our findings, it may mean that we have underestimated the effects of TC and HDL-C and, hence, the extent to which they attenuate the association between TG and MI risk. In addition, our study does not include data on LDL-cholesterol, nor on insulin resistance, lipoproteins or particle size, all factors that have an impact on TG [13]. The duration of elevated TG might have been too short to translate into a clinical end-point such as MI, so we cannot exclude the possibility that elevated TG for more than 7–10 years is associated with a greater risk of MI. Finally, as this is an observational study,

we cannot capture information on other changes to patient management and/or lifestyles that may have had an impact on MI risk.

The large reduction in RR from 1.67 to 1.11 suggests that a large proportion (if not all) of the effect seen in univariable analyses is due to confounding. Additional adjustments for DM and fasting glucose levels did not modify the RR further, but did result in wider confidence intervals and non-significant associations. Furthermore a causal link between TG level and MI cannot be established due to the observational nature of our study.

The importance of understanding whether high levels of TG preceded or followed the presence of cardiovascular risk factors is not yet clear. As elevated TG are often seen in many conditions associated with inflammation (e.g. CVD, fatty liver disease), elevated TG might be a non-specific biomarker rather than an independent risk factor for MI or CVD and therefore likely more affected in HIV-positive subjects, in whom ongoing inflammation is not infrequent, compared to the general population.

Conclusion

Given the ageing of the HIV population, and their potential lifelong reliance on antiretroviral therapy, it has become essential to identify patients at risk for MI and CVD, allowing prevention measures to be targeted more appropriately. Based on our results, we suggest that future risk stratification should be focused more closely on non-TG lipids such as TC and HDL-C, and on other and modifiable CVD risk factors, including smoking.

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