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ORIGINAL PAPER

Statins and Aspirin use in HIV-infected people: gap between European AIDS Clinical Society guidelines and clinical practice: the results from HIV-HY study

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Abstract
Objectives To investigate the use of statins and acetylsalicylic acid (ASA) in HIV people in clinical practice.
Design A multicenter, nationwide, prospective cohort study, including 1182 consecutive HIV patients was conducted.
Methods Statin and ASA prescription was evaluated in primary and secondary cardiovascular disease prevention, according to the European AIDS Clinical Society (EACS) guidelines.
Results Followed-up patients (998) were mostly males (70.9 %) with a mean age at enrolment of 46.5 years (SD 9.5). The mean time of follow-up was 3.3 years (SD 0.8). At the last follow-up visit, statins would have been recommended for 31.2 % and ASA for 16 % by EACS guidelines. Conversely, only 15.6 and 7.6 % of patients were on statin and ASA treatment, respectively; only 50.3 % of patients treated with statins achieved recommended low-density lipoprotein cholesterol (LDL-c) levels. At the last follow-up visit, agreement between statin therapy and EACS recommendation was 0.58 (95 % CI 0.52–0.63). The corresponding figure for ASA therapy was 0.50 (95 % CI 0.42–0.58), whereas the agreement for ASA therapy in secondary prevention was 0.59 (95 % CI 0.50–0.68).
Conclusions The prescription of statins and ASA in HIV-infected patients remains largely suboptimal, as only about 50 % of patients requiring statins and ASA are properly treated. Higher attention on this relevant issue and further investigation are warranted in this at risk population.

Keywords HIV · Statin · Aspirin · Antiretroviral therapy · Cardiovascular prevention · Framingham · Cardiovascular disease · Atherosclerosis · Clinical

The CISAI study group members are listed in Acknowledgments section.

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Introduction

As HIV-infected individuals get a longer life expectancy than in the past, cardiovascular disease (CVD) is emerging as an important cause of morbidity and mortality. Even under antiretroviral therapy (ART), HIV-infected patients present a higher risk of myocardial infarction and cardiovascular (CV) death than age-matched uninfected controls [1]. As a consequence, traditional CV risk factors, such as dyslipidemia, smoking and the metabolic syndrome (MS), remain key objectives for prevention strategies [2–4]. Current international guidelines mandate preventive interventions for lifestyle modification, as well as pharmacological interventions on blood pressure, glucose and lipid levels, to improve CV prognosis in HIV-infected patients [5, 6]. Given the expected CVD risk and the proven benefit of statins in reducing clinical events across numerous patient groups, timely administration of statins might be particularly beneficial in a large proportion of HIV patients with dyslipidemia. However, safety concerns and dearth of data on clinical outcomes in HIV-infected patients on simultaneous ART and statin therapy may have so far contributed to limit statin use in HIV-infected patients chronically on ART [7]. The European AIDS Clinical Society (EACS) version 6.1, available at the time of the present study, recommended the use of statin in patients with established CVD or type 2 diabetes or CVD risk ≥20 % and LDL >115 mg/dL; similarly ASA was recommended in patients with previous CVD or aged ≥50 years and at high (≥20 %) 10-year CVD risk [5]. Some reports underline, however, the underutilization of ASA in HIV patients and few data are available on use of statins and ASA in such a setting in clinical practice [8, 9].

In the present study, to our knowledge for the first time in this specific setting, we aimed at assessing the level of concordance between EACS recommendations and prescription of statins and ASA in an unselected sample of HIV-infected patients enrolled at several Italian sites.

Methods

Characteristics of the sample and study design

The study was conducted by the Coordinamento Italiano per lo Studio di Allergia e Infezione da HIV (CISAI, Italian coordination group for the study of allergies and HIV infection). Patients were enrolled in the HIV-HY study as previously reported [10] and followed up for up to 4 years. In brief, from May 2010 through May 2014, 1182 adult HIV patients attending scheduled or unscheduled outpatient visits at hospital sites involved in the CISAI group were enrolled. Sex, age, anthropometric measures, smoking habits, arterial blood pressure (BP), history of diabetes, lipodystrophy, chronic hepatitis, and HIV stage according to the Centers for Disease Control classification, use of lipid-lowering drugs, antihypertensive, ASA were all recorded using a standardized data collection form. Laboratory tests included absolute CD4+ T-lymphocyte count and fasting total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides, blood glucose and creatinine levels. The diagnosis of hypertension and diabetes, as previously reported [10], was based on standard international criteria [11, 12]. Patients receiving anti-diabetic or BP-lowering medications were classified as having diabetes and hypertension, respectively. The patients were followed up over time, to evaluate cardiovascular risk modifications due to therapeutic and lifestyle interventions.

Statin prescription was evaluated in primary and secondary prevention, according to EACS Guidelines 6.1 available at enrolment and follow-up [5]; of note, the EACS Guidelines refer to ATPIII Guidelines with regard to the prescription of statins for patients with CVD risk <20 % [13]. The 10-year Coronary Heart Disease (CHD) risk was evaluated using the Framingham point scores [13]. If the HDL-C value was missing, we assigned point = 0 in the calculation of Framingham point score. According with Framingham CHD risk stratification, CV risk was categorized as low for CHD <10 %; intermediate for CHD 10–20 %; high for CHD ≥20 %.

ASA eligibility was evaluated according to the EACS recommendations, that is in patients with previous CVD and in patients aged ≥50 years and high 10-year CVD risk (≥20 %). As in the general population, the ASA eligibility in primary prevention is still a matter of debate [14], and we separately considered indications for primary and secondary prevention.

Outcomes

The primary outcome measure was prescription of drugs associated with CVD risk modification: statins and ASA. The specific drug or dose and the time of the original prescription were not taken into account.

The secondary outcome measure was whether patients treated with statin attained LDL-c EACS recommended targets (≤115 mg/dL). Therefore, we categorized patients with indication to statin: not on statin, not at LDL-c target; on statin not at LDL-c target; on statin at LDL-c target.

Statistical analysis

Continuous variables were described as means (standard deviations, SD) or medians (interquartile range, IQR), ordinal and categorical variables as frequency (%). Continuous variables were compared using the analysis of variance or

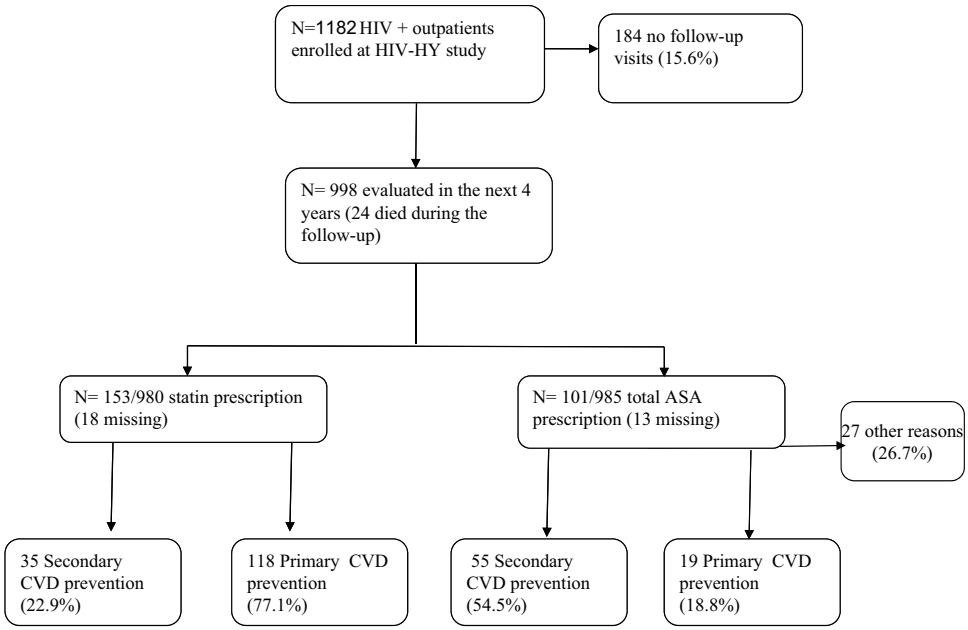

Fig. 1 Recruitment and flowchart in cohort of HIV + patients. Prescription of statin and aspirin (ASA) at last follow-up in primary and secondary prevention

the Mann–Whitney *U* test as appropriate. In the crude analysis, we used the heterogeneity χ^2 test (or the Mantel-Hanszel χ^2 test as appropriate) to assess the association between groups and categorical variables. Odds ratios (ORs) and the corresponding 95 % confidence intervals (CI) were used to evaluate the association between statins/ASA use, or achieving target LDL, and patients' characteristics and clinical variables potentially associated. We ran multivariate analyses including potential confounders in the equation, as indicated in table footnotes or specified in the text.

Data analysis was conducted with SAS for Windows 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Recruitment of patients and the flowchart of the study are shown in Fig. 1. Overall, 998 patients out of 1182 (84.4 %) had at least 1 follow-up visit. The proportion of patients lost to follow-up from baseline was 15.6 %. In this sample, males represented 70.9 %. Mean age at enrolment was 46.5 years (range 18–78, SD 9.5). Nine hundred and twenty-one (92.3 %) patients were Caucasian and 5.9 % and 1.5 % were ART naïve at enrolment and last visit, respectively. The mean time of follow-up was 3.3 years (SD 0.8). Demographic and clinical characteristics of the whole group at baseline and last visit are presented in Table 1.

Statin recommendations and prescription

Information on statin use was available for 948 and 980 patients at enrolment and follow-up, respectively. Statins would have been recommended in 228 (24.0 %) and 306 (31.2 %) patients, respectively. At baseline, 85 subjects (37.3 %) were prescribed statins out of 228 with indication, 17 in secondary and 68 in primary prevention. At follow-up, 153 (50.0 %) out of 306 with indication were prescribed statins; 35 in secondary and 118 in primary prevention (Fig. 2a).

The kappa agreement between guideline recommendations and actual prescriptions was 0.47 (95 % CI 0.41–0.54) and 0.58 (95 % CI 0.52–0.63) at baseline and follow-up, respectively.

The percentages of patients for different CHD risk groups on statin therapy referred to the percentages of subjects in need of statin treatment are depicted in Fig. 3. Interestingly, the lowest proportion of treatment was observed among patients at intermediate CHD risk.

LDL-c target

LDL-c target achievement is a readily available benchmark for dyslipidemia control. At baseline, 28 (32.9 % of those treated) patients achieved the recommended LDL-c level, whereas 54 did not; 143 were untreated. Information on LDL goal was missing in 3 subjects. At last visit, 77 (50.3 % of those treated) patients on statin treatment achieved the recommended LDL-c level: 53.6 % of those with high 10-year CHD risk (HR), 53.6 % of those at intermediate risk (IR) and 44.4 % of those at low risk (LR). The LDL-c target in patients on statin therapy at baseline and follow-up is shown in Fig. 4a, b.

At univariate analysis, achieving LDL-c target with statin therapy was more frequent in ex-smokers, hypertensive

Table 1 Patients' characteristics at baseline and last visit ($N = 998$)

	Baseline		Follow-up	
	N or mean or median	% or SD or IQR	*N* or mean or median	% or SD or IQR
Age, y	46.5	9.5	49.8	9.5
Time on study (years)	–	–	3.3	0.8
Gender				
M	708	70.9	708	70.9
F	290	29.1	290	29.1
BMI, Kg/m^2	24.4	3.9	24.6	4.0
HIV risk factor				
IVDU	214	21.4	214	21.4
Sexual transmission	703	70.4	703	70.4
Other*	81	8.1	81	8.1
Smoking				
N	381	38.2	357	35.8
Y	469	47.0	469	47.0
Ex	148	14.8	172	17.2
CDC stage#				
A	448	45.7	411	42.2
B	250	25.5	266	27.3
C	282	28.8	298	30.6
Naive	59	5.9	15	1.5
HIVRNA undetectable	765	77.4	821	82.3
CD4+ count/ml	567	409–772	631	467–855
Metabolic syndrome	318	31.9	296	29.7
Diabetes	45	4.5	56	5.6
Hypertension	313	31.4	421	42.2
On treatment	159	15.9	279	28.0
Untreated	154	15.4	142	14.2
Systolic BP, mm Hg	123.5	14.4	122.8	14.0
Diastolic BP, mm Hg	78.7	9.7	77.4	8.9
Glucose, mg/dl	91.4	20.1	92.5	20.7
Total cholesterol, mg/dl	201.0	43.8	201.8	42.0
LDL cholesterol, mg/dl	119.2	38.3	117.2	37.4
HDL cholesterol, mg/dl	46.7	15.2	48.3	16.0
Triglycerides, mg/dl (median, IQR)	135	92–199	129	91–191
10-years CHD risk %	4.0	1.0–10.0	6.0	2.0–16.0
eGFR, ml/min	96.9	25.1	96.1	28.1
Chronic HCV infection	252	25.2	214	21.4

* Vertical transmission, transfusion, IVDU + sexual, undetermined (other)

CDC Stage was not reported in 18 cases at baseline and in 23 cases at follow-up

IVDU intravenous drug users, *CHD* Framingham coronary heart disease risk, *eGFR* estimated Glomerular filtration rate

patients, subjects with MS or hepatitis C virus (HCV) coinfection, as well as in older patients. At multivariate analysis, adjusting for age, smoking habits, hypertension status, MS and HCV coinfection, age (OR 1.65, 95 % CI 1.13–2.41) by 10 years and HCV coinfection (OR 3.74, 95 % CI 1.18–11.83) were significantly related to achieving LDL-c target. As to ART, no significant relation was observed with ART class, although LDL target was achieved more frequently in patients on integrase inhibitors (INIs) (57.1 vs 47.8 %) and was inversely related to the number of ART drugs (60.0 % in patients taking 1–2 drugs, 50.0 % in those taking 3 drugs, 46.8 % in those on 4 or more drugs).

Aspirin recommendation and prescription

Information on ASA use was available for 950 and 985 patients at enrolment and follow-up, respectively. Among them, at baseline 100 (10.5 %) subjects were candidates to ASA treatment, 44 (4.4 %) as secondary prevention; at follow-up, the corresponding figures were 160 (16.0 %) and 75 (7.6 %). The agreement between EACS indications and actual ASA treatment was lower at baseline than at follow-up (kappa = 0.36, 95 % CI 0.26–0.46 and kappa = 0.50, 95 % CI 0.42–0.58). A similar situation was observed when considering secondary prevention only (kappa = 0.45, 95 % CI 0.32–0.58 vs kappa = 0.59, 95 % CI 0.50–0.68).

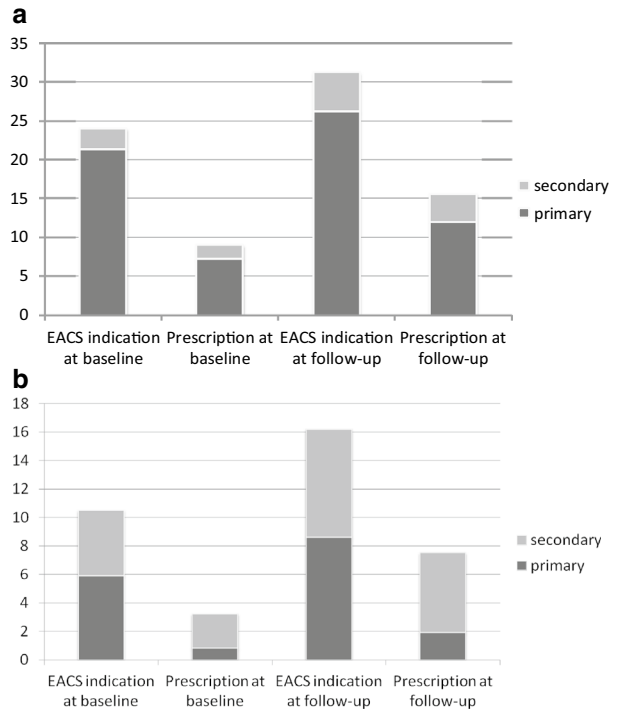

Fig. 2 The agreement between recommendation of statin (**a**) and aspirin (**b**) according to the European AIDS Clinical Society (EACS) guidelines and real life prescription. Baseline and last follow-up (FU) data from HIVHY study

According to EACS guidelines, 85 patients (8.6 %) at last visit were candidates for primary prevention, and 75 (7.6 %) for secondary prevention. We could not establish, however, the EACS indication to ASA in 27 (2.7 %) subjects, on ASA treatment. Reasons were as follows: subclinical atherosclerosis i.e. carotid plaques (5), general practitioner opinion/high CHD risk perception (14); polycythemia (1); recurrent venous thrombosis/pulmonary embolism (1), valvular heart disease (2); missing information (4). ASA indications (EACS and secondary prevention) and prescription at baseline and follow-up are shown in Fig. 2b.

Clinical practice prescription of statin and aspirin

We performed multivariable analyses to identify the characteristics of HIV patients for which these drugs were indeed prescribed by clinicians. As expected, at univariate analysis traditional risk factors such as age, hypertension, smoking, previous CVD event, high estimated Framingham risk and lower estimated Glomerular Filtration Rate (eGFR), were strongly associated with prescription. These results were controlled including adjustment factors in the logistic regression model. Chronic HCV infection was inversely

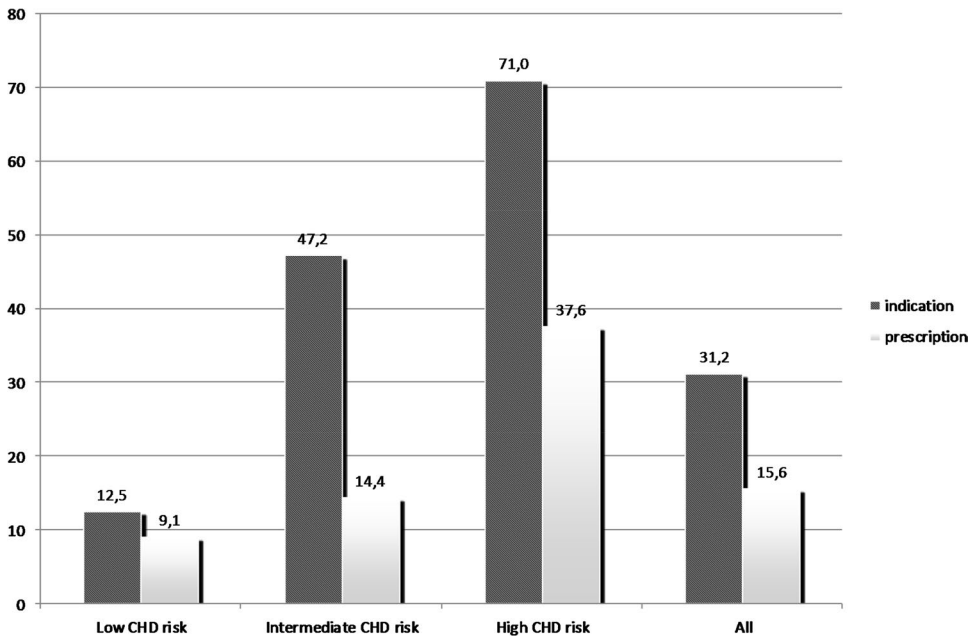

Fig. 3 Cardiovascular risk stratification (Framingham coronary heart disease risk: low CHD <10 %; intermediate CHD 10–20 %; high CHD ≥20 %) and statin recommendations according to the European AIDS Clinical Society (EACS) guidelines compared with clinical practice prescriptions

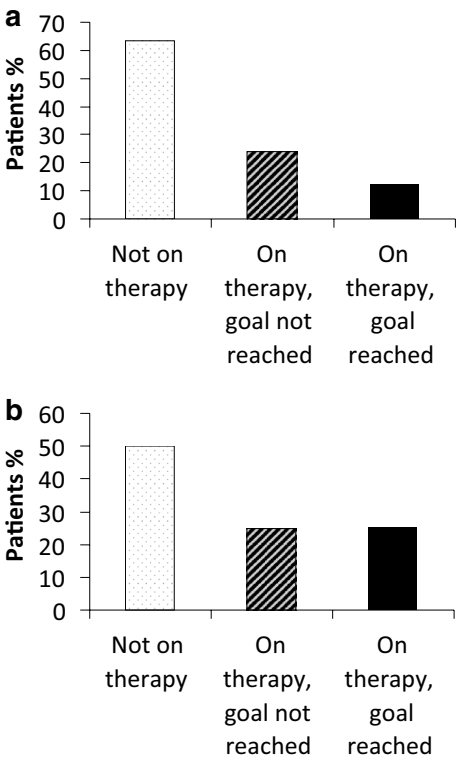

Fig. 4 LDL-c target in patients with statin indication according to EACS guidelines at baseline (**a**) and at last follow-up (**b**)

associated with statin prescription, though not significantly (AOR 0.63, 95 % CI 0.31–1.30, $p = 0.21$).

We investigated the relation between statin prescription and ART. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) were inversely associated with statin prescription (41.2 % in subjects not on statin therapy, 30.1 % in patients on statin therapy), whereas the opposite occurred for INIs use (16.3 vs 27.4 %). No difference was observed for protease inhibitors (PIs).

Among patients with EACS indication, age, hypertension, major CVD events, statin use and lower eGFR were associated with ASA prescription at univariate analysis. Including these factors in a logistic regression equation, we confirmed that CVD events (AOR 19.58, 95 % CI 7.29–52.64, $p < 0.0001$) and statin use (AOR 4.66, 95 % CI 1.77–12.25, $p = 0.002$) represented significant determinants of ASA use.

No differences were found when considering regimens including PIs, INIs, NNRTIs, or a high number of drugs. On the other hand, ASA prescription was less frequent in females, in current smokers, in CDC stage C subjects, and in patients with chronic HCV infection. None of these relationships, possibly due to the small sample size, achieved statistical significance.

Discussion

The study analyzed a large, unselected sample of Italian HIV-infected patients, mostly on ART, observed in routine outpatient clinical care, to assess the real life use of ASA and statins in HIV people. The evaluation of the correspondence between EACS international cardiovascular disease prevention and management guidelines and clinical practice demonstrated that patients in care for HIV infection were treated with statins or ASA in less than half of the indicated cases. There is no specific study exploring adherence to CV preventive recommendations comparing HIV and non-HIV patients. However, in a recent large Italian survey on the general Italian population, among 5626 patients with indication for lipid-lowering interventions according ATP III criteria, 71 % were on statin therapy [15]. The present study therefore reinforces concerns that implementation of current guidelines for CV prevention in HIV people is far from appropriate, at least in Italy. Statin therapy is the main pharmacological intervention to treat dyslipidemia, widely used across the globe for the treatment and prevention of CVD, and it is well established that statin therapy is associated with a significant decrease in plasma cholesterol levels and CVD mortality [16]. Moreover, statin treatment was associated with several anti-inflammatory, immunological and pleiotropic effects, leading to a decrease in serum concentrations of inflammatory markers and a slower atherosclerosis progression, potentially beneficial in HIV-infected patients [17]. This study reinforces the idea that the use of lipid-lowering therapy in HIV people remains widely suboptimal in primary and secondary CVD prevention. This is especially true looking at the new guidelines, released more recently. In November 2013, the theoretical eligibility for lipid-lowering therapy in the general population was extended by the American College of Cardiology/American Heart Association (ACC/AHA) recommendations [18]. The newly released EACS guidelines 8.0 in 2015 [19] similarly extended statin therapy for patients with CHD risk $\geq$10 %.

Suboptimal prevention seems to be associated with various factors. Interestingly, chronic HCV infection was more frequent in subjects with indication without prescription (19.2 vs 13.1 % in patients on statin). Caution is suggested when statin treatment is prescribed in subject with liver disease; thus, physicians' concern as to aggressive prescription of statins in comorbid HIV-infected patients with abnormal liver function may in part explain such an observed association. However, as recent data showed that drug-induced liver injury from statins is rare, underutilization of statins among HIV patients may well be related to fears on potential drug–drug interactions with some antiretroviral, as well

as on reduced patient's adherence to multiple pharmacologic treatments [20].

Another major finding of the present study is that statin therapy, although appropriate, is not adequately targeted by physicians: LDL-c target was obtained in only 50.3 % of patients treated with statins. The reason for the suboptimal achievement of the LDL-c target in HIV-infected patients could descend from the concurrent use of drugs associated with an LDL-c increase (such as ritonavir-boosted PIs), as well as to poor patient's adherence to the lipid-lowering treatment [21]. This relevant finding may not represent a true estimate of the problem, because investigators at sites participating in the HIV-HY study are particularly aware of CVD risk, thus vigorously promoting risk reduction through behavioral and therapeutic interventions. As a consequence, changes in CV risk factors in this cohort may be somewhat greater than in other settings of Italian and international clinical practice. However, the LDL-c goal achieved in the present study was not worse than that reached in the general population, according to recent studies [15, 22, 23]. In fact, in our cohort 77 patients (50.3 %) reached the EACS standard target LDL-c (<115 mg/dL) level, while other reports from general population in Italy showed that the target of LDL-c <100 mg/dL was reached in 34–53 % of treated patients [15, 22, 23].

Patients at higher CV risk received, as expected, preventive treatment more frequently; at variance, the lowest proportion of patients on statin treatment was found among patients at intermediate CHD risk. Therefore, a higher attention on CV prevention strategies might yield a greater benefit in such a setting [24, 25].

As the indication for ASA primary prevention is still debated in the general population [26], we used a more conservative approach, focusing on secondary CVD prevention. Indeed, the evidence supporting ASA for secondary CV prevention in the general population is stronger: in high risk patients ASA reduces the yearly risk of serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) by about a quarter [27]. The use of ASA in secondary CVD prevention was 91 % in coronary patients from EUROSPIRE III, a large survey from 22 European countries [28] and 51.7 % in a survey from 400 Italian general practitioners on 35,473 patients with previous CVD [29]. In our study, at the last follow-up visit, the ratio between subjects on ASA and those who needed ASA for secondary CVD prevention was 55/75 (73.3 %). Comparing with the EACS guidelines on ASA recommendation, the gap between indication and prescription is even more relevant.

Even so, a direct comparison between HIV and non-HIV-infected people was not possible. However, considering comparable published data in different settings, underprescription of ASA and statins in Italian HIV patients, in the real life scenario, is very likely.

Although suboptimal CV risk factor control is similarly common in HIV-uninfected people, the implication of these findings may be more serious in HIV-infected subjects, given their additional CV risk factors [30, 31]. However, we observed an increased number of patients treated with statins as well as ASA during follow-up, which may represent an interesting signal of increasing attention and awareness by prescribing clinicians, and an improvement of general CV prevention over time, in line with a previous report [32].

The management of dyslipidemia in the aging HIV-infected population will represent a formidable challenge in CV health policy [33]. Our findings suggest an urgent need to set up and deploy further interventions to equip all HIV providers with the scientific evidence and will to tackle the increasingly complex demands of comprehensive HIV care, particularly in light of the rising importance of HIV associated non-AIDS (HANA) conditions in the aging HIV population [34]. Understanding and optimizing preventive care in HIV people is essential in maintaining the substantial advances in prognosis for patients living with HIV infection.

The main strength of our study was the inclusion of an unselected multicenter sample of Italian HIV-infected patients assisted at current sites of ordinary care, which is likely to represent the general assisted HIV population. The most relevant limitations in our present work include the observational design of the study, the absence of a parallel control group of uninfected individuals, as well as the absence of information regarding adherence to statin and ASA therapy. The number of patients without follow-up visit is a further limitation.

In conclusion, clinical management of lipid-lowering therapy was inadequate in many HIV-infected patients, as more than half of the patients in need were untreated. This finding may have important implications as to the impact of cardiovascular disease in this population. A higher level of attention to traditional risk factors and their treatment is warranted in the setting of HIV infection.

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Compliance with ethical standards

Conflict of interest No conflict of interest in this paper.

Ethics Patients were enrolled in the HIV-HY study as previously reported [10]. Informed consent was not required by the ethics committee, because confidentiality was guaranteed and no interventions were performed.

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