

Short communication

Use of statins and aspirin to prevent cardiovascular disease among HIV-positive patients. A survey among Italian HIV physicians

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SUMMARY

We conducted a survey among Italian HIV specialists to study the utilization of statins and aspirin, administering a questionnaire aimed at investigating their use, the use of guidelines and scores, and the management of interactions.

The answers were uniform in the different geographic areas. The majority directly prescribe statins and 43% of them prescribe aspirin. The majority follows guidelines and utilize scores to calculate the CV risk.

Our survey demonstrates the commitment and autonomy in prescribing statins and aspirin of Italian physicians. There is a rationale to generate guidelines to overcome the differences and limitations among current recommendations.

Running title: Use of statins and aspirin among HIV-positive patients.

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The introduction of combined antiretroviral therapy (cART) regimens has had a major impact on the natural history of HIV infection, leading to a dramatic decrease in its mortality and a considerable increase in the life expectancy of people living with HIV (PLWHIV). Nevertheless, these patients still appear to be at higher risk of a number of co-morbidities, such as CVD, than the general population (Nou *et al.*, 2016; Martin-Iguacel *et al.*, 2015; Freiberg *et al.*, 2013). The etiology of the increased risk is still not completely understood, but endothelial activation due to the chronic inflammation may play a pivotal role in CVD events (Durand *et al.*, 2011). Statins and aspirin have a pivotal role in reducing the morbidity and mortality of CVD. The effect of statins and aspirin in preventing CVD is linked to their anti-inflammatory activity on vessels and, consequently there is a stronger rationale in their use among PLWHIV. However the current guidelines (The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS 2011; ACC/AHA, 2013) for the use of these drugs in the general population are dissimilar, with important differences between American and European recommendations, and the guidelines for PLWHIV reflect this scenario resulting sometimes incomplete. Regarding PLWHIV, the European AIDS Clinical Society (EACS) version 8, recommends the use of statin in patients with established CVD or type 2 diabetes or 10-year CVD risk $\geq 10\%$ irrespective of lipid levels. Similarly aspirin is recommended in patients with previous CVD or aged ≥ 50 years and at high ($\geq 20\%$) 10-year CVD risk (EACS guidelines, version 6.1; 2011). However, some reports emphasize the underutilization of aspirin in HIV patients and few data are available on use of statins and aspirin in such a setting in clinical practice (Tornero *et al.*, 2010; Burkholder *et al.*, 2012). Also, a recent Italian study found that the prescription of statins and aspirin in HIV-infected patients remains largely suboptimal, as only about 50% of patients requiring statins and aspirin are properly treated (De Socio *et al.*, 2016). For this reason, we conducted a survey among Italian HIV specialists to investigate the use of these drugs in the real life setting and understand if there is the need for specifically addressed guidelines for HIV-positive patients.

A self-administered questionnaire was sent to all physicians committed to outpatient care and directly responsible for drug prescription (both antiretrovirals and co-administration therapies for HIV-associated non-AIDS conditions) among 27 infectious disease units in Italy from November 2015 to January 2016. The questionnaire was based on the following ten points, investigating their use of statins and aspirin, the use of specific guidelines, scores and parameters driving their choices and the management of drug-drug interactions (DDIs).

1) Do you directly prescribe/suggest statins in your PLWHIV when appropriate? The following answers were possible: a) Yes, b) No, I refer my patients to other specialists if I think they need statins c) No, I do not treat cardiovascular risk in my PLWHIV.

2) Do you follow any guideline to evaluate the opportunity of prescribing statins in your PLWHIV? The following answers were possible: a) Yes, b) No.

3) If yes, which one? The following answers were possible: a) EACS HIV, b) Italian HIV Guidelines, c) American College of Cardiology/American Heart Association (ACC/AHA) 2013.

4) If not, how do you evaluate the opportunity of prescribing statins in your PLWHIV? The following answers were possible: a) Based on total cholesterol, b) Based on LDL-C, c) Based on estimated cardiovascular risk, d) In the presence of co-morbidity (e.g., diabetes).

5) Do you directly prescribe/suggest aspirin in your HIV patients when appropriate? The following answers were possible: a) Yes, b) No, I refer my patients to other specialists if I think they need aspirin c) No, I do not treat cardiovascular risk in my PLWHIV.

6) Do you utilize any score to calculate the cardiovascular risk of your PLWHIV? The following answers were possible: a) Yes, b) No, I evaluate the risk factors (blood pressure, cholesterol, smoke, diabetes) without the use of scores, c) No, I do not evaluate cardiovascular risk factors at all.

7) If yes, which one? The following answers were possible: a) FRS, b) ASCVD, c) Data Collection on Adverse events of Anti-HIV Drugs (DAD), d) Progetto Cuore.

8) Do you prescribe statins in patients with subclinical atherosclerosis diagnosed by coronary artery calcium (CAC) or intima-media thickness (IMT)? The following answers were possible: a) Yes, b) No.

9) Before prescribing a statin do you evaluate the DDIs with antiretroviral therapy? The following answers were possible: a) Yes, b) No.

10) In case of DDIs do you... The following answers were possible: a) Abandon the statin therapy? b) Change the statin? c) Consult a cardiologist?

For the questions 3, 4 and 7 multiple answers were admitted.

The participants were 128 Italian HIV physicians. All the physicians filled out the questionnaire. Of them 33 were from North, 43 from Central and 52 from South Italy. As shown in Table 1, 89% directly prescribe or suggest statins, while 43% prescribe or suggest aspirin. The remaining physicians refer the patient to other specialists. 73% follow guidelines for prescribing statins, mainly Italian guidelines (46%), followed by EACS-HIV (35%) and ACC/AHA 2013 (19%). Those who do not follow guidelines prescribe statins based on LDL-C (36%), estimated CV risk (34%), or presence of co-morbidities (21%), while total cholesterol is rarely used (9%). 58% utilize scores to calculate CV risk: the vast majority use FRS (71%) followed by DAD (12%), ASCVD (13%) while only 4% use

Progetto Cuore; 50% prescribe statins also in case of subclinical atherosclerosis; 97% consider DDIs between statins and cART and, in case of DDIs, 49% change the statin, 38% consult the cardiologist and 13% abandon the statin. Table 1 also shows the differences between the three geographic areas.

Results from several studies have suggested that PLWHIV have an increased risk of CVD, especially coronary heart disease, compared with people not infected with HIV. The incidence of CVD overall in HIV is relatively low, but it is approximately 1.5-2-fold higher than that seen in age-matched HIV-uninfected individuals. PLWHIV are exposed both to an increased prevalence of traditional CVD risk factors, and to HIV-specific mechanisms such as inflammation (Nou *et al.*, 2016; Martin-Iguacel *et al.*, 2015). The early and continuous use of current cART, which might have fewer metabolic effects, minimizes the risk of myocardial infarction by maintaining viral suppression and decreasing immune activation. Even with cART, however, immune activation persists in PLWHIV and could contribute to accelerated atherosclerosis (Hsue *et al.*, 2009; Calmy *et al.*, 2009; Friis-Møller *et al.*, 2010; Neuhaus *et al.*, 2010; Durand *et al.*, 2011; Hsue, 2012; Freiberg *et al.*, 2013). Therefore, treatments that safely reduce inflammation in PLWHIV could provide additional cardiovascular protection alongside treatment of both traditional and non-traditional risk factors.

About thirty years ago, statins ushered in the era of lipid lowering as the most effective way to reduce risk of atherosclerotic cardiovascular disease. More recently it has been demonstrated that statins, through their HMG-CoA reductase inhibitor activity, have pleiotropic immunomodulatory properties that contribute to their benefit in atherosclerosis beyond lipid lowering (Walter *et al.*, 2002; Shapiro and Fazio, 2016).

On the other hand, aspirin remains one of the most extensively studied cardiovascular medications in the history of medicine. The drug reduces the incidence of myocardial infarction (MI), stroke, and vascular death in patients with vascular disease via its antiplatelet activity. However, despite multiple, well-designed, large randomized controlled trials evaluating the potential of aspirin to prevent cardiovascular events in individuals without known CVD, the role of aspirin in primary prevention is currently unclear. The initial aspirin trials included largely low-risk individuals with primary outcomes mostly focused on MI and stroke, and showed a significant reduction in these CVD outcomes, especially MI. The more recently conducted trials have focused on older, higher CVD risk populations with high rates of lipid-lowering and antihypertensive medication use. These studies have used broader CVD outcomes as their primary end points and have failed to show a significant benefit of aspirin therapy in primary prevention. The exact reasons for the lack of efficacy in these recent trials are unclear but may be related to the low rate of atherothrombotic events relative to other CVD events in the populations studied (Miedema *et al.*, 2016). The evidence supporting aspirin 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 (Antithrombotic Trialists' Collaboration, 2002). However, nowadays aspirin is recommended in secondary CV prevention as well for men aged 45 to 79 years when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage and for women age 55 to 79 years when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage (Maciosek *et al.*, 2006; Mosca *et al.*, 2007; US Preventive Services Task Force, 2009).

For the use of statins in CVD prevention, the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidaemias (The Task Force for the management of dyslipidaemias of the ESC and the EAS, 2011) suggest evaluating the total CV risk of the subjects using European SCORE tables, identify the LDL-C target for that risk level, calculate the percentage reduction of LDL-C required to achieve that goal, and choose a statin that, on average, can provide this reduction. For these guidelines, since the response to statin treatment is variable, up-titration to reach the target is mandatory. If the statin cannot reach the goal, they suggest considering drug combinations.

Unlike European guidelines, the ACC/AHA identified four statin benefit groups in which the potential for an atherosclerotic CVD (ASCVD) risk reduction benefit clearly exceeds the potential for adverse effects (1-individuals with clinical ASCVD; 2- individuals with primary elevations of LDL-C ≥ 190 mg/dL; 3-individuals 40 to 75 years of age with diabetes with LDL-C 70-189 mg/dL; 4-individuals without clinical atherosclerotic CVD or diabetes who are 40 to 75 years of age with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher), identified high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention and suggested the appropriate intensity of statin therapy to reduce ASCVD risk in those most likely to benefit. On the other hand, this Expert Panel was unable to find evidence to support continued use of specific LDL-C and/or non-HDL-C treatment targets. Finally, this guideline recommends use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk (ACC/AHA 2013).

Some European authors took a stand against ACC/AHA guidelines, objecting that if generally adopted, they will result in an increase in the number of patients treated, potentially at considerable cost. Moreover, the new pooled mixed cohorts equation used to assess ASCVD risk has been validated in an American population, different from European countries, and requires more careful evaluation if applied in other contexts (Ray *et al.*, 2014). In summary, the debate between American and European guidelines is still open.

To the best of our knowledge, this is the first survey performed on HIV specialists on this topic. Due to the high number of participants it can be considered a representative sample. The answers were uniform in the three geographic areas and demonstrate a great commitment toward CVD comorbidity. In fact, the majority of physicians directly prescribe statins and 50% of them directly prescribe aspirin, the remainder consult a specialist. None declare they did not treat the CVD of their HIV patients (answers 1 and 5). The majority follow guidelines for statin prescription (mainly the Italian Guidelines, followed by EACS, but cardiologic guidelines ACC/AHA are not infrequently consulted). The physicians who declare they do not follow guidelines base their prescription mainly on evaluation of CVD risk and LD-Cc levels. The majority utilize scores to calculate the CV risk of their patients (mainly FRS followed by DAD). Also in this case, ASCVD cardiologic guidelines are not infrequently consulted. 50% of the physicians directly prescribe statins in case of subclinical atherosclerosis. The risk of DDIs with statins is widely considered. The majority of the Italian HIV specialists directly choose a different statin in case of DDIs.

Some minor differences emerged comparing the three different geographic areas. Physicians in Southern Italy tend to refer patients to other specialists if they think they need statins or aspirin with respect to their colleagues in Northern and Central Italy, and evaluate the CV risk based on the single risk factors while their Northern and Southern colleagues use scores more frequently. Moreover, physicians in Southern Italy tend to utilize Italian guidelines more frequently while Northern and Center physicians prefer EACS guidelines and Central physicians frequently also consult the ACC/AHA.

In conclusion, our survey demonstrates the high attention of Italian HIV physicians to CVD, and their commitment and autonomy in prescribing statins and aspirin. Consequently, in the light of the previously discussed discrepancies among the different guidelines and the incomplete indications regarding HIV-positive persons, there is a strong rationale to generate specific guidelines for HIV patients able to overcome the differences and limitations among current recommendations.

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Table 1: Results of the survey divided for the different geographic areas.

	Total (#128) % (#)	North (#33) % (#)	Center (#43) % (#)	South (#52) % (#)
1) Do you directly prescribe/suggest statins in your HIV patients when appropriate?				
Yes	89 (114)	91 (30)	95 (41)	83 (43)
No, I refer my patients to other specialists if I think they need statins	11 (14)	9 (3)	5 (2)	17 (9)
No, I do not treat cardiovascular risk in my HIV patients	0	0	0	0
2) Do you follow any guideline to evaluate the opportunity of prescribing statins in your HIV patients?				
Yes	73 (94)	70 (23)	77 (33)	73 (38)
No	27 (34)	30 (10)	23 (10)	27 (14)
3) If yes, which one?*				
EACS HIV	35 (37)	44 (11)	42 (16)	24 (10)
Italian HIV Guidelines	46 (48)	36 (9)	26 (10)	69 (29)
ACC/AHA 2013	19 (20)	20 (5)	32 (12)	7 (3)
4) If not, how do you evaluate the opportunity of prescribing statins in your HIV patients?*				
Based on total cholesterol	9 (5)	13 (3)	7 (1)	14 (3)
Based on LDL cholesterol	36 (21)	33 (8)	40 (6)	34 (7)
Based on estimated cardiovascular risk	34 (20)	29 (7)	33 (5)	38 (8)
In the presence of co-morbidity (e.g., diabetes)	21 (12)	25 (6)	20 (3)	14 (3)
5) Do you directly prescribe/suggest aspirin in your HIV patients when appropriate?				
Yes	43 (55)	61 (20)	53 (23)	23 (12)
No, I refer my patients to other specialists if I think they need aspirin	57 (73)	39 (13)	47 (20)	77 (40)
No, I do not treat cardiovascular risk in my HIV patients	0	0	0	0
6) Do you utilize any score to calculate the cardiovascular risk of your HIV patients?				
Yes	58 (74)	73 (24)	67 (29)	40 (21)

No, I evaluate the risk factors (blood pressure, cholesterol, smoke, diabetes) without the use of scores	42 (54)	27 (9)	33 (14)	60 (31)
No, I do not evaluate cardiovascular risk factors at all	0	0	0	0
7) If yes, which one? *				
Framingham Score	71 (69)	71 (22)	65 (26)	81 (21)
ASCVD	13 (12)	16 (5)	12 (5)	8 (2)
DAD	12 (12)	3 (1)	20 (8)	11 (3)
Progetto Cuore	4 (4)	10 (3)	3 (1)	0
8) Do you prescribe statins in patients with subclinical atherosclerosis diagnosed with CAC or IMT?				
Yes	50 (64)	36 (12)	44 (19)	38 (20)
No	50 (64)	64 (21)	56 (24)	62 (32)
9) Before prescribing a statin do you evaluate the drug-drug interactions with the antiretroviral therapy?				
Yes	97 (124)	91 (30)	98 (42)	100 (52)
No	3 (4)	9 (3)	2 (1)	0
10) In case of drug-drug interactions do you				
Abandon the statin therapy?	13 (17)	21 (7)	19 (8)	4 (2)
Change the statin?	49 (59)	43 (14)	46 (20)	50 (25)
Consult a cardiologist?	38 (52)	36 (12)	45 (15)	46 (25)

*=multiple answers admitted