Eleggibilità e prescrizione delle statine nei pazienti con infezione da HIV in Italia.

Eligibility and prescription of statins in people living with HIV from Italy.

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Riassunto

Le attuali line guida internazionali indicano degli interventi di prevenzione, tra cui l'uso di farmaci ipolipemizzanti per migliorare la prognosi cardiovascolare nei PLWH (people living with HIV).
Scopo di questa analisi era indagare l'uso delle statine nei PLWH nella pratica clinica, in uno studio di coorte

Abstract

Current international guidelines mandate preventive interventions, including lipid lowering drugs, to improve cardiovascular prognosis in people living with HIV infection (PLWH). The Objective of this study was to investigate the use of statins in PLWH in clinical practice, in a multicenter, nationwide, prospective

prospettico, multicentrico, nazionale; il campione si basa sui 1620 PLWH arruolati nel progetto SCOLTA. La prescrizione delle statine è stata valutata come prevenzione cardiovascolare primaria e secondaria, secondo le linee guida dell'American College of Cardiology/American Heart Association (ACC/AHA) Cholesterol Management. La concordanza tra indicazioni delle linee guida ed effettiva prescrizione è stata valutata tramite il coefficiente kappa. Secondo le caratteristiche al basale, 745 (42.1%) di PLWH erano candidabili alla statina e 226 (12.8%) erano in trattamento. Durante il follow-up, 128 (5.6%) pazienti in più hanno incontrato i criteri per iniziare il trattamento con statina e 99 (7,0%) l'hanno iniziato. Complessivamente, in tutto il periodo di studio, 873 (49,3%) dei pazienti affetti da HIV erano candidati alla terapia con statina e 325 (18,4%) facevano già terapia con statine o l'hanno iniziata. La concordanza tra indicazione al trattamento con statina secondo le linee guida ACC/AHA e le attuali prescrizioni è stata 0,31 (95% CI 0.27-0.34) al basale e 0.37 (95% CI 0.34-0.40) all'ultima visita del follow-up. In conclusione, nella coorte SCOLTA 49,3% era eleggibile al trattamento con statina secondo le linee guida ACC/AHA e il 18.4% ha iniziato il trattamento. Il livello di concordanza con le raccomandazioni pertanto resta basso.

cohort study, sampling 1620 consecutive HIV people enrolled in the SCOLTA project.
Statin prescription was evaluated as primary and secondary prevention for cardiovascular disease (CVD), according to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Cholesterol Management Guidelines. The agreement between indication and prescription was evaluated using the kappa coefficient.
According to their baseline characteristics, 745 (42.1%) PLWH were candidates to statins. At baseline, 226 (12.8%) were on treatment. Over the follow-up time, 128 (7.2%) more PLWH met the criteria for statin treatment indication, and 99 (5.6%) started a new statin treatment.
Overall, in the whole study period 873 (49.3%) PLWH were candidates to statin treatment, and 325 (18.4%) were on or started a statin. The kappa agreement between indication to statin treatment and actual prescription was 0.31 (95% CI 0.27-0.34) at baseline and 0.37 (95% CI 0.34-0.40) at the last follow-up visit. In the SCOLTA cohort 49.3% of PLWH were statin-eligible according ACC/AHA Cholesterol Management Guidelines and 18.4% initiated treatment. The level of concordance with these recommendations was low.

Introduction

People living with HIV (PLWH) have now a longer life expectancy than in the past, so cardiovascular disease (CVD) emerged as an important cause of morbidity and mortality. Even under antiretroviral therapy (ART), HIV-infected patients have a higher risk of myocardial infarction and cardiovascular (CV) death than age-matched uninfected controls (1). Traditional CV risk factors, such as dyslipidemia, smoking and the metabolic syndrome (MS) remain key objectives for prevention strategies both in HIV and non-HIV people (2, 3). Hypercholesterolemia has been recognized as an important and modifiable risk factor for CV diseases. 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. The recommendations for lipid-lowering treatment initiation are based on the curvilinear relation between LDL-C and CVD risk and the evidence from randomized clinical trials (RCTs) demonstrating the efficacy of statins for primary prevention of CVD (4, 5). 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.

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Cholesterol Management Guidelines broadened clinical indications for statins compared with previous ATP III guidelines (6), resulting in increased eligibility (7). In the general population, is known a gap between eligible and treated patients, with a substantial proportion of persons with indication who not receiving statins (8).

Some reports emphasize the underutilization of statin in HIV patients in clinical practice (9). In Italy also, the prescription of statins in HIV-infected patients was largely suboptimal in a report including patients from 2010 through 2014, as only about 50% of patients requiring statins are properly treated (10). We aimed at assessing the level of concordance among international recommendations and prescribing practice of statins in HIV-infected patients enrolled in SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretrovirals/antivirals) project at several Italian sites in the last eight years. We analysed patients enrolled in the SCOLTA cohorts since 2014, when

new guidelines for statin treatment were published by the American College of Cardiology/American Heart Association (ACC/AHA) (7).

Methods

We analysed data from the SCOLTA prospective database. The SCOLTA project, a multicentre observational cohort study, started in 2002 and prospectively follows PLWH who start treatment with new antiretroviral drugs, to identify toxicities and AEs in a real-life setting (11). The SCOLTA project utilises an on-line pharmacovigilance program (www.cisai.it) and currently involves 30 Italian Infectious Disease Centres.

Briefly, both ART-naïve and ART-experienced PLWH can be included in SCOLTA, if they are >18 years and agreed to enter the study. Clinical data collected include sex, age, ethnicity, weight, height, CDC stage, and previous ART history. Laboratory data include HIV-RNA, CD4 +T cell count, and biochemical data, and are prospectively collected in anonymous form in a central database every six months. AEs are collected prospectively as soon as they are clinically observed.

Enrolled patients were considered statin-eligible per ACC/AHA guidelines if they diagnosed with CVD (or had ASCVD score >20.0); or were diabetic and between the ages of 40 and 75 years; or had an LDL ≥190 mg/dL; or had a 10-year risk of CVD (defined as incidence nonfatal myocardial infarction, death because of coronary heart disease, or stroke) of 7.5% or more and were between the ages of 40 and 75 years. Ten-year risk calculations (ASCVD) were derived from pooled cohort equations (7).

We evaluated indication and prescription in 3 strata: low CVD risk if Ten-year risk calculations by ASCVD was <7.5%; intermediate risk if ASCVD was between 7.5% and 19.99% and high risk if ASCVD was 20% or more or if were diagnosed with major CVD.

Information on concomitant pharmacological treatments and comorbidities are collected at baseline and updated every six months.

The original study protocol was approved on 18 September 2002, and new protocol amendments were approved on 13 June 2013, 20 December 2019 and 3 March 2020, by the coordinating centre at Hospital "L. Sacco"-University of Milan, Milan (Italy) and thereafter by all participating centres. Written consent for study participation was obtained from all participants, and the study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and by Italian national laws.

Statistical analysis

Data were described using mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for not normally distributed continuous variables and frequency (%) for categorical and ordinal variables.

A logistic regression analysis was performed to evaluate the risk of taking a statin when primary or secondary prevention was indicated (odds ratio, OR, and 95% confidence interval, CI). The multivariate model included potential confounders.

The agreement between ACC/AHA guidelines and clinical prescription was evaluated using the kappa coefficient.

All Ps were two-sided, at the significance level <0.05. Statistical analyses were performed using SAS for Windows 9.4 (SAS Institute, Cary, NC).

Results

Overall, 3481 PLWH were included in several cohorts. After excluding those with missing response to any variable needed to calculate the ASCVD score, we selected 1939 subjects, 1769 with at least one follow-up visit (**Figure 1**): darunavir (n=171), elvitegravir (n=213), rilpivirine (n=193), dolutegravir (n=741), bictegravir (n=329), or doravirine (n=122) cohort. The median follow-up time was 22 months (IQR 12-37).

One thousand and twenty-four PLWH (57.9%) had no indication to statins at baseline, 230 (13.0%) had indication for secondary prevention and 515 (29.1%) indication for primary prevention: 39 were aged 40-75 years and had diabetes, 107 had dyslipidaemia, 406 were aged 40-75 years with CVD risk ≥ 7.5%. Some of them had more than one indication to statin treatment. The characteristics of PLWH in study are reported in **Table 1**.

According to their baseline characteristics, 745 (42.1%) PLWH were candidates to statins. At baseline, 226 (12.8%) were on treatment. Over the follow-up time, 128 (7.2%) more PLWH met the criteria for statin treatment indication, and 99 (5.6%) started a new statin treatment.

Overall, in the whole study period 873 (49.4%) PLWH were candidates to statin treatment, and 325

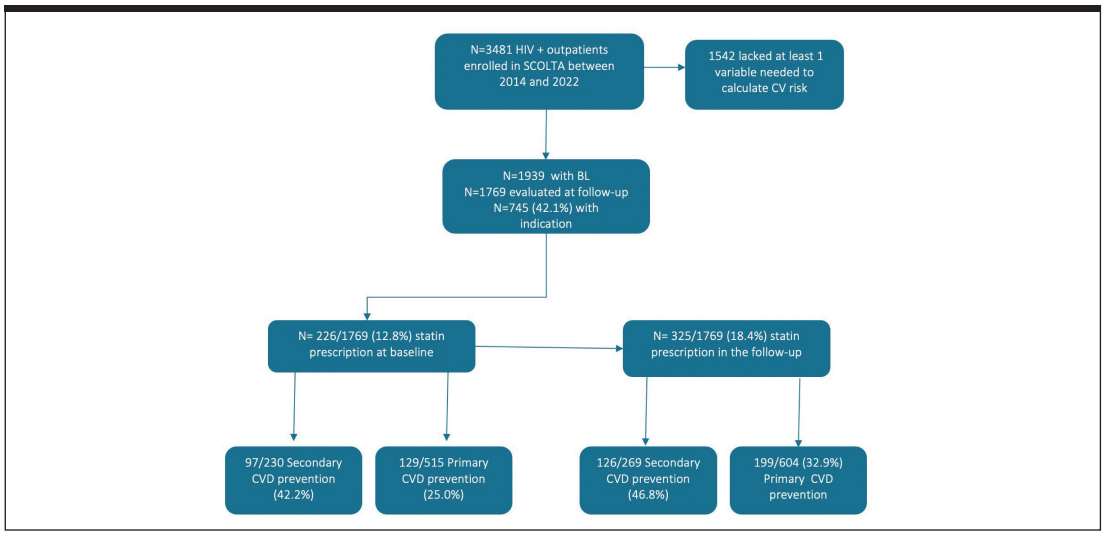

Figure 1. Patients enrolled from SCOLTA project.

	Baseline		Follow-up	
	N or mean or median	**% or SD or IQR**	**N or mean or median**	**% or SD or IQR**
Age	48.3	11.9	50.6	12.0
Time on study (months)	22	12-37		
Gender				
M	1324	74.8		
F	445	25.2		
Caucasian	1615	91.3		
BMI	24.6	4.2	25.1	4.4
HIV risk factor				
IVDU	332	18.8		
Sexual transmission	1265	71.5		
Other*	172	9.7		
Smoking				
N	622	35.2		
Y	841	47.5		
Ex	306	17.3		
CDC Stage#			(14 missing)	
A	882	49.9	892	50.4
B	512	28.9	496	28.0
C	375	21.2	367	20.8
Naive	318	18.0		
HIVRNA undetectable	1244/1451	85.7	1535/1675	93.3
CD4+ cells/mm^3	592	384-824	680	471-910
Metabolic syndrome	570/1747	32.6	381/1174	32.4
Diabetes	103	5.8	126	7.1
Hypertension				
-on treatment	357	20.2	430	24.3
-untreated	54	3.1	47	2.7
Total Cholesterol, mg/dl	189	45	188	44
LDL Cholesterol, mg/dl	113	38	112	37
HDL Cholesterol, mg/dl	48	17	50	15
Triglycerides, mg/dl (median, IQR)	117	85-167	109	79-156
10-years CVD risk%	4.3	1.4-10.3	4.7	1.7-10.8
eGFR ml/min	93	26	84	26
Chronic HCV infection (RNA positive)	128	7.2	46	2.6
ART cohort				
Bictegravir	329	18.6		
Darunavir	171	9.7		
Dolutegravir	741	41.9		
Doravirina	122	6.8		
Elvitegravir	213	12.0		
Rilpivirine	193	10.9		

**vertical transmission, transfusion, IVDU+sexual, undetermined (other)*
Framingham coronary heart disease risk (CHD)
estimated Glomerular Filtration Rate (eGFR)

Table 1. Patients' characteristics at baseline and last visit (N=1620).

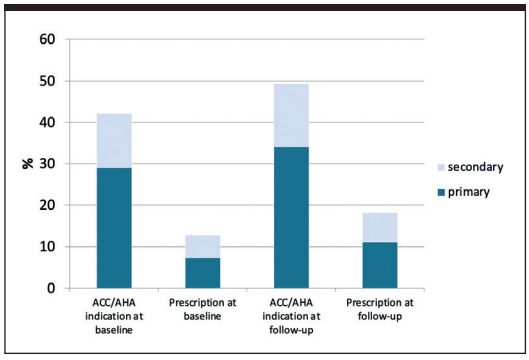

Figure 2. Candidates to treatment in primary or secondary prevention and actual treatment at baseline and last visit.

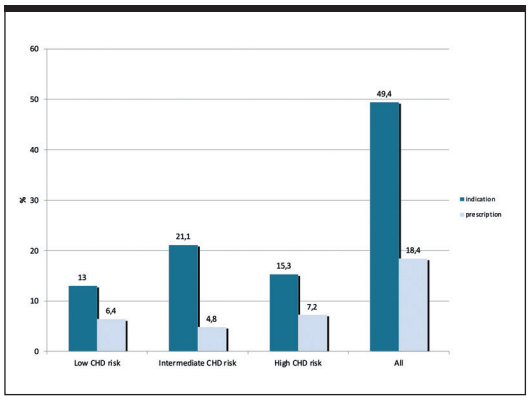

Figure 3. Indication and prescription in patients according to cardiovascular risk.

(18.4%) were on or started a statin.

Candidates to treatment in primary or secondary prevention and actual treatment at baseline and at last visit are reported in **Figure 2**. The kappa agreement between indication to statin treatment and actual prescription was 0.31 (95% CI 0.27-0.34) at baseline and 0.37 (95% CI 0.34-0.40) at the last follow-up visit.

In **Figure 3** the number of PLWH eligible and treated are reported according to strata of cardiovascular risk (ASCVD score <7.5%, 7.5-19.9%, ≥20%).

The differences between indications and prescription is highest in patients with intermediate CV risk strata. Using the high-risk stratum as the reference, PLWH at low risk were as likely to receive statins (OR 0.83, 95% CI 0.56-1.22), but PLWH at intermediate risk were significantly less likely on therapy (OR 0.31, 95% CI 0.20-0.48).

In **Table 2** the adjusted odds ratios (AOR) for the risk of taking statins are reported, in a model including all the variables in the table, with the exception of age and estimated Glomerular Filtration Rate (eGFR), that were alternatively included.

Women and people with hypertension, treated or untreated, or with high CV risk (ASCVD score > 20 or previous CVD event) are more likely to be prescribed statins, whereas people with chronic HCV infection and current smokers are less frequently treated. As shown in **Figure 4**, the proportion of PLWH on statin treatment increased over the years but declined in the most recent considered period (2020-2022).

Discussion

The suboptimal implementation of prevention strategies and uncontrolled atherosclerotic CV risk factors in many adults remains among the leading cause of CV morbidity and mortality. Among PWH in care enrolled in the SCOLTA project from January 2014 to September 2022, the gap between PLWH eligible for statins and those initiating statins persists over time. The proportion of patients with a statin indication who received a prescription was less than half among those with an indication based on ACC/AHA guidelines. The most difficult to treat patients were people with chronic HCV infection and current smokers. The gap in treatment among HCV-coinfected patients could be related to provider concern regarding potential hepatotoxicity. However, a positive trend of prescription was observed over the year from 2014 to 2019. Interest, in the last years 2020-2022 the decline of statin prescription could be related to more difficult access at ambulatory care linked to Covid-19 pandemic.

The study underscores the low agreement from guideline and current clinical practice and reinforces concerns that implementation of current guidelines for CV prevention in PLWH from Italy is far from appropriate. Statin therapy is the main pharmacological intervention to treat dyslipidemia, widely used 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 (4). 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.

Patients at higher CV risk received, preventive treatment more frequently; at variance, the lowest

Effect	No statin (n=548, 62.8%)		Statin (n=325, 37.2%)		AOR§	95% Confidence Limits		P
Age (mean, SD, OR by 10 years)	55.2	9.3	56.0	9.4	0.97	0.88	1.07	0.54
Sex (ref. M) F	458 70	87.2 12.8	251 74	77.2 22.8	1.68	1.13	2.49	0.01
Smoking (ref: no) Current Former	139 334 75	25.4 61.0 13.7	118 129 78	36.3 39.7 24.0	 0.59 1.39	 0.41 0.89	 0.84 2.39	0.0001
Hypertension (ref. no) - on treatment - untreated	366 158 24	66.8 28.8 4.4	164 144 17	50.5 44.3 5.2	 1.81 1.68	 1.28 0.85	 2.57 3.30	0.003
CVD risk (ref. LR) - IR - HR	249 215 84	45.4 39.2 15.3	167 80 78	51.4 24.6 24.0	 0.66 1.16	 0.44 0.70	 0.97 1.91	0.02
CVD event (ref. No event)	66	12.0	71	21.9	1.32	0.84	2.07	0.23
eGFR (mean, SD, by 5 points)	89	26	84	23	0.99	0.96	1.02	0.50
Chronic HCV infection	59	10.8	11	3.4	0.28	0.14	0.57	0.0005
InIs (ref. No InIs use)	639	80.1	270	83.1	1.24	0.76	2.02	0.38
NNRTIs (ref. No NNRTIs use)	130	23.7	76	23.4	1.26	0.80	1.97	0.32
PI (ref No PI use)	87	15.9	56	17.2	1.22	0.74	1.99	0.44
Calendar years of enrollment 2014-2015 2016-2017 2018-2019 2020-2022	 133 144 93 178	 24.3 26.3 17.0 32.5	 65 82 93 85	 20.0 25.2 28.6 26.2	 1.00 1.28 1.91 0.79	 0.79 1.20 0.52	 2.07 3.04 1.22	 0.0009

CVD risk: low CVD <7.5% (LR); intermediate CVD 7.5-19.9% (IR); high CHD ≥ 20% (HR).
Cardiovascular diseases (CVD), estimated Glomerular Filtration Rate (eGFR), integrase inhibitors (INIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
eGFR and age were alternatively used.

Table 2. Factors associated with statin use among patients with indication at any time from baseline to last follow-up (n=873).

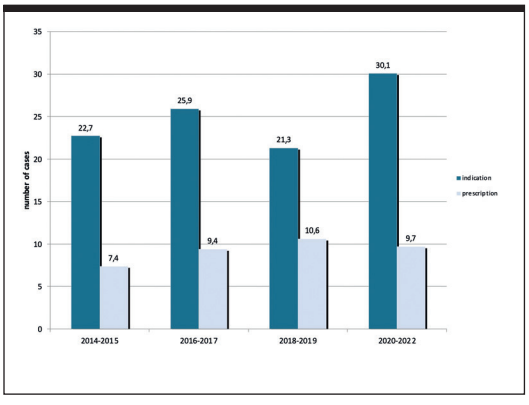

Figure 4. Indication and prescription by enrollment period.

proportion of patients on statin treatment vs theoretical indication was found among patients at intermediate CVD risk. Therefore, a higher attention on CV prevention strategies might yield a greater benefit in such a setting. Our results are in line with a recent report from North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), they found that on 2014, 51% of patients were statin-eligible and 25% initiated treatment. The authors speculate that whether this gap between indication and prescription of statin represents a true deficiency in care, is reflective of complex medical needs of PWH who are aging, and have a high prevalence of age-related comorbidities, multimorbidity and polypharmacy. And that the introduction of statins may not be a priority because of increased pill burden or interaction with medications (12).

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, the absence of information regarding adherence to statin, details of the specific prescribed drugs and relative doses of therapy. The statin indications in guidelines were changed over time, however we evaluated only the accordance with 2013 indication as released just before the study observational period, independently from subsequent modifications.

In conclusion, this study demonstrates that more than half of HIV-infected primary care patients had an indication for statin therapy based on the ACC/AHA dyslipidemia treatment guidelines. Clinical management of lipid lowering therapy was discordant compared with these indications in many HIV-infected patients, as widely more than half of the patients were untreated.

The management of dyslipidemia in the aging HIV-infected population still represent a formidable challenge in CV health policy. A higher level of attention to traditional risk factors and their treatment is warranted yet in the setting of HIV infection. ■

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