Comparative safety and efficacy of statins for primary prevention in human immunodeficiency virus-positive patients: a systematic review and meta-analysis

Comparative safety and efficacy of statins for primary prevention in HIV-positive patients: A systematic review and meta-analysis

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ABSTRACT.

Introduction. Efficacy and safety of different statins for HIV-positive patients in primary prevention remain to be established, along with the potential impact of HIV control and treatments on them.

Methods and Results. In the present meta-analysis, 18 studies including 736 HIV-positive patients on highly active anti-retroviral therapy (HAART) treated with statins in primary prevention were short-listed (21.0% women, median age 44.1, min-max (36.3,56.0)). Total cholesterol change, the primary end-point, was higher with rosuvastatin 10 mg and atorvastatin 10 mg (mean -1.67, 95% confidence interval [CI](-1.99,-1.35) mmol/l and -1.44, 95%CI(-1.85,-1.02) mmol/l, respectively). Secondary end-points were: LDL change, more marked with rosuvastatin 10 mg (mean -1.12, 95%CI(-1.40,-0.83) mmol/l), atorvastatin 80 mg (mean -2.10, 95%CI(-3.39, -0.81) mmol/l) and simvastatin 20 mg (mean -1.57, 95%CI(-2.67, -0.47) mmol/l); HDL increase, greater with pravastatin 10-20 mg, rosuvastatin 10 mg and atorvastatin 10 mg; triglycerides reduction, obtained more decisively by rosuvastatin 10 mg, atorvastatin 10 and 80 mg and simvastatin 20 mg. Mean discontinuation rate was 0.12 per 100 person-years (95% CI (0.05,0.20)), and was higher with atorvastatin 10 mg (26.5 per 100 person-years, 95% CI (13.4,64.7)). A meta-regression analysis shows that nucleoside reverse transcriptase inhibitors (NRTI)-sparing regimens were associated with reduced efficacy considering total cholesterol, HDL cholesterol (along with non-NRTI-containing regimens) and triglycerides.

Conclusion. Statin therapy significantly lowers cholesterol values in HIV-positive patients with a satisfying safety profile. HAART, despite well-characterized drug-to-drug interactions, do not affect the effectiveness and safety of dose-adjusted statins, as the only significant interaction reported was an enhanced lipid-lowering effect with NRTIs.

Keywords: HIV-positive patients, cardiovascular risk, statin therapy, antiretroviral therapy, dyslipidaemia.

INTRODUCTION.

Human Immunodeficiency Virus (HIV) positive patients are exposed to a higher risk of cardiovascular (CV) adverse events, which represent the leading cause of death in this population, especially after the introduction of highly active antiretroviral therapy (HAART). The increased risk is related to the complex interaction between CV risk factors, to the deregulation of auto-immunity and to the target therapy itself (1-5)

For HIV-positive patients, it is crucial to both assess and reduce CV risk, even more than it is for HIV-negative patients. Hyperlipidemia represents a frequent finding, driven by negative lifestyle habits, HAART therapy, and the virus itself (6-8). For example, protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTI) may be associated with a syndrome of abnormal fat redistribution marked by peripheral fat wasting and central adiposity (9.)

While an aggressive diet has shown some promising results, statins (HMG-CoA Reductase Inhibitors) (9,10) have become crucial and are widely used, thanks to their efficacy to reduce cholesterol and to the pleiotropic effects regarding plaque stabilization and regression (11).

Current evidence, however, is fraught by the absence of data on the most efficacious statin, the potential interaction with HAART and the rate of discontinuation due to side effects (12). Consequently we performed a systematic review and meta-analysis to offer physicians an accurate overview of the safety and efficacy of statin use in HIV-positive patients in the HAART era.

METHODS.

To elaborate the present manuscript, we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA), the amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement along with recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE). To perform the Network Meta-Analysis, the National Institute for Health and Care Excellence Decision Supporting Unit (NICE DSU) guidelines were followed (13-18).

Search strategy

Two researchers (SG, FDA) searched on Medline/Pubmed, Cochrane Library, Biomed Central, and Google Scholar for pertinent articles published in English according to the following strategy, with established methods and incorporating wild cards (identified by *) with the following terms: ((statin) OR (HMG-CoA reductase inhibitors) OR (atorvastatin) OR (rosuvastatin) OR (cerivastatin) OR (fluvastatin) OR (lovastatin) OR (mevastatin) OR (pitavastatin) OR (simvastatin)) AND (hiv OR aids OR (human AND immunodeficiency AND virus)) NOT (review[pt] OR editorial[pt] OR letter[pt]).

Study selection

All citations were discussed by two co-authors (SG; FDA) at the title and/or abstract level, with divergences resolved after consensus. If potentially pertinent, they were appraised as complete reports. Inclusion criteria were (all had to be present): (i) human studies, (ii) HIV-positive patients treated with statin in primary prevention (iii) ≥ 6 weeks follow-up. Exclusion criteria included: (i) non-human setting, (ii) duplicate reporting (in which case the manuscript reporting the largest sample of patients was included) and (iii) less than 75% of patients on HAART.

Data extraction

For each paper, two co-authors (SG; FDA) elaborated these clinical features: authors, journal, year of publication, location of the study group, baseline, CV and HIV features, kind and dose of statin.

Absolute change of total cholesterol was the primary end-point, while variation of LDL cholesterol, HDL cholesterol and triglycerides and treatment discontinuation due to any adverse event the secondary ones.

Impacts of age, CD4 cell counts, BMI, HAART (divided by regimens including at least one PI [PI-containing regimens, from now on], regimens including at least one non nucleoside reverse transcriptase inhibitors [NNRTI-containing regimens, from now on] and regimens not including NRTIs [NRTI-sparing regimens, from now on]) length of follow up, time from HIV diagnosis and HAART exposure duration were tested at meta-regression analysis. Sensitivity analysis was performed for kind of statin, and after including also randomized controlled trials.

Internal validity and quality appraisal

Two unblinded reviewers (SG, FDA) evaluated the quality of the studies on pre-specified electronic forms, with divergences resolved after consensus. According to the MOOSE, we separately abstracted and appraised study design, setting, data source, as well as (in keeping with the Cochrane Collaboration approach) the risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, high risk of bias, or incomplete reporting leading to inability to ascertain the underlying risk of bias).

Data analysis and synthesis

Continuous variables are reported as mean (± standard deviation [SD]) or as median (± interquartile range [IQR] or minimum and maximum value) as appropriate. Total cholesterol, LDL, HDL and triglycerides values are expressed as mmol/l, where 1 mmol/l of total cholesterol, LDL or HDL corresponds to 38.67 mg/dl and 1 mmol/l of triglycerides to 88.57 mg/dl.

Statistical pooling for incidence estimates was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals (CI) by using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Study bias was appraised by graphical inspection of funnel plots. Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and was based on the Cochran Q test, with I^2 values of 25%, 50%, and 75% representing mild, moderate, and extensive statistical inconsistency respectively.

Network meta-analysis was performed with random-effect models (derived from NICE DSU statement (18)) with OPenBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). Each analysis was based on non-informative priors for effect sizes. Convergence and lack of auto-correlation were checked and confirmed after a 100,000-simulation burn-in phase, and, finally, direct probability statements were based on an additional 500,000-simulation phase. Deviance and deviance information criterion (DIC) were used to appraise model fit. Results of network meta-analysis were reported as odds ratios (OR) with 95% CI for categorical variables and mean differences (WMD) with 95% CI for continuous variables. Extent of small study effects/publication bias was assessed by visual inspection of funnel plots.

Metaregression analysis was performed with Comprehensive Meta-Analysis, reporting results as Beta, i.e. regression coefficients.

RESULTS.

The systematic literature search produced 236 citations that were screened and evaluated at the abstract level (Figure 1). Of these, 37 were appraised as full text, among which 19 were excluded: six for not stratifying results by statin type and dose (8,19-23), four for not assessing cholesterol variations (24-27) three for including patients not on HAART (10,28,29), two for < 100% patients on statin (30,31), two for duplicate reporting (32,33), one for reporting variations of lipid profile after poly-pharmacologic therapy (34), one for reporting values not suitable for the present analysis (35). Finally, 18 studies were included, of which two utilized pravastatin 10-20 mg (36,37), nine pravastatin 40 mg (38-46), seven rosuvastatin 10 mg (37,39,42,47-50), two atorvastatin 10 mg (37,42), one atorvastatin 20-40 mg (51), one atorvastatin 80 mg (52), one fluvastatin 20-40 mg (36) and one simvastatin 20 mg (53).

A total of 736 patients were included (see Table 1), of whom 21.0% were female, with a median age of 44.1 years (min-max (36.3, 56.0)) and mean BMI of 23.9 (IQR (23.3,25.1)). At baseline (Table 2), median CD4 cell count was 521 cells/mm^3 (IQR (430,551)), mean time from HIV diagnosis was 107 months (IQR (75.3,118.8)) and average duration of HAART exposure was 69.1 months (IQR (62.0, 97.0)). The median follow up was 12 weeks (IQR (12,36)).

All patients were on HAART: 76.5% PI-containing regimens, 29.8% on NNRTI-containing regimens, and 16.2% on NRTI-sparing regimens.

Rosuvastatin 10 mg and atorvastatin 10 mg were the two statins associated with higher variation in total cholesterol levels (mean -1.67 mmol/l, 95% CI (-1.99,-1.35) and mean -1.44 mmol/l, 95% CI (-1.85,-1.02), respectively, see figure 2), while rosuvastatin 10 mg (mean -1.12, 95% CI (-1.40,-0.83)), atorvastatin 80 mg (mean -2.10, 95% CI (-3.39,-0.81)) and simvastatin 20 mg (mean -1.57, 95% CI (-2.67,-0.47)) reported the most notable changes in LDL cholesterol (Figure 3). Relative reductions, expressed as percentage, of total cholesterol and LDL are reported in Supplementary Table 3. Higher

increases in HDL cholesterol were observed in patients receiving pravastatin 10-20 mg (mean 0.24 mmol/l, 95% CI (0.10,0.38)), rosuvastatin 10 mg (mean 0.10 mmol/l, 95% CI (0.04,0.17)) and atorvastatin 10 mg (mean 0.15 mmol/l, 95% CI (0.07,0.23), Supplementary Figure 1). Triglycerides values significantly changed (Supplementary Figure 2) in patients treated with rosuvastatin 10 mg (mean -0.56, 95% CI (-0.70,-0.42)), atorvastatin 10 mg (mean -0.59, 95% CI (-0.81,-0.37)) and 80 mg (mean -0.60, 95% CI (-1.09,-0.11)) and simvastatin 20 mg (mean -0.61, 95% CI (-1.14,-0.08)).

Mean discontinuation rate due to adverse events was 0.12 (95% CI (0.05,0.20)) per 100 person-years overall, with the higher incidence occurring with atorvastatin 10 mg (mean 26.5 per 100 person-years, 95% CI (13.4,64.7), Figure 4).

All results were consistent when including randomized controlled trials only; however rosuvastatin 10 mg lost its significant correlation with HDL increase after this adjustment (data not shown).

Meta-regression analysis (see Supplementary Table 2) shows that NRTI-sparing regimens were associated with a smaller decrease in total cholesterol (Beta 0.007, 95% CI (0.001,0.013), p value 0.018, Figure 5) and that HDL cholesterol increase was negatively affected by age (Beta -0.009, 95% CI (-0.016,-0.003), p value 0.005), NNRTI-containing regimens (Beta -0.002, 95% CI (-0.002,-0.001), p value < 0.001) and NRTI-sparing regimens (Beta -0.001, 95% CI (-0.002,-0.001), p value < 0.001, Supplementary Figures 3-5). Eventually, a smaller reduction of triglycerides was reported in older patients (Beta 0.030, 95% CI (0.002,0.058), p value 0.035), in patients on NRTI-sparing regimens (Beta 0.006, 95% CI (0.002,0.011), p value 0.007) and in those with a longer time from HIV diagnosis (Beta 0.005, 95% CI (0.003,0.008), p value < 0.001, Supplementary Figures 6-8), while no significant interactions were found for LDL and discontinuation relating to adverse events.

Network meta-analysis for total cholesterol did not show significant differences among treatments, but it was possibly limited by the inclusion of only 4 RCTs for total cholesterol and 5 for the other end-points (Supplementary table 3).

The methodological assessment revealed an overall satisfactory quality of the included studies, the vast majority being prospective, a third multi-centre, without a high risk of analysed bias; geographical origin of study was heterogeneous with the majority being performed in Europe (see Supplementary Figure 9 and Supplementary table 4).

DISCUSSION.

The main findings of the present analysis are that

1) Statins significantly reduce total cholesterol, LDL and triglycerides in HIV-positive patients on HAART, with rosuvastatin 10 mg figuring as the most reliable molecule in all tested areas based on the amount and consistency of evidence proving its effectiveness and safety.

2) Statins have a limited efficacy for increasing HDL

3) Despite their risk of pharmacokinetic interactions (especially with PIs), statins and HAART are safe and effective when concomitantly administered in this population.

Since the introduction of HAART, HIV-positive patients' life expectancy has dramatically increased, reaching values comparable to that of the general population (54); in this aging population, non-traditionally AIDS-related illnesses, like CV disease (CVD), have become a major clinical issue (55,56). Patients affected by HIV are more prone to developing CVD (57,58), especially ischemic heart disease (59), with higher rates of acute coronary syndromes (60), frequently presenting as ST-segment myocardial infarction, and high intra-hospital and one-year mortality rates, as compared to HIV-negative controls (61). Moreover, ischemic heart disease often occurs in these patients at earlier stages in life (62)

Although the exact mechanism for the increased CV risk is not fully understood, it is ascertained that both traditional risk factors and HIV-related factors are potential contributors, with smoking and dyslipidaemia representing the most important traditional CV risk factors (63). HIV infection itself and HAART therapy significantly alter lipid metabolism, and lipodystrophy/lipoatrophy are well known side effects of HAART (64), which may adversely affect CV outcomes as well as adherence to HIV treatment (65). More specifically, HIV infection is usually associated with increased serum

triglycerides (66) and lower levels of HDL, LDL and total cholesterol (67-69), while HAART is principally characterised by augmented levels of total cholesterol, LDL and triglycerides and decreased levels of HDL (66), with slightly different patterns varying according to the different combinations of the antiretroviral drugs employed (63). All classes of HAART have been reported to affect lipid metabolism (70,71): higher levels of triglycerides and cholesterol have been associated with PIs and efavirenz (67) even if these effects are significantly attenuated with newer PIs and NNRTIs (72), augmented values of HDL, LDL and triglycerides have been reported with PIs (73), while NRTIs have showed a larger variability of effects depending on the specific molecule tested (74). In this scenario, PIs have been the drugs more consistently and heavily associated with lipid metabolism alterations, particularly with hypercholesterolemia, hypertriglyceridemia and lipodystrophy. Several mechanisms have been proposed to explain this class-effect of PIs and they include retinoic acid and LDL binding protein metabolism alterations (75), increase in hepatic triglycerides synthesis (76) and glucose transporter type 4 (GLUT-4) interference (with reduced insulin sensitivity) (77). However it should be noted that, among the commonly used PIs, only lopinavir/ritonavir has been associated with an increase risk of cardiovascular disease (63). Finally, as a further manifestation of altered lipid metabolism in HIV-positive patients, recent studies reported a significantly higher prevalence of cardiac steatosis, assessed by cardiac magnetic resonance (CMR) with spectroscopy (78) and a higher prevalence of non-calcified plaques in HIV-positive patients as compared to controls (79).

Despite the undeniable relevance of this topic, no definite reference values of lipid levels have to date been defined in this population, as there are no statements from major scientific societies providing clear indications. In a conjunct statement, the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group suggested an individual target for lipid values based on the Framingham 10-year cardiovascular risk score, referring, as target values, to those applied to the general population

based on the Adult Treatment Panel III (NCEP ATP III) cholesterol guidelines (80). The 2011 European Society of Cardiology/European Atherosclerosis Society lipid guidelines, while acknowledging the increased risk related to dyslipidaemia in HIV patients and claiming the need for group-tailored targets, failed to provide specific cut-offs due to the lack of validated, prospective data on lipid levels and CV events in HIV-positive patients (81).

Treatment of dyslipidaemia has been attempted with non-pharmacological interventions, (i.e. diet or lifestyle-changing interventions) (82), or by switching HAART medications (68,83). Despite these remedies, a lipid-lowering therapy is often needed: a prescription rate of HMG-CoA reductase inhibitors (i.e. statins) varying from 8.3 to 15.5% has been reported (84,85), but it has been estimated that, to comply with current guidelines (86), a statin therapy should be prescribed up to 19-26% of consecutive patients aged 18-60 years without known CVD undergoing coronary computed tomography (87).

In HIV-positive patients, however, statins have been tested mostly in small studies. Clear-cut data on their efficacy and safety are still lacking, and to date no study, to the best to our knowledge, has prospectively assessed the effectiveness of this therapy in primary prevention on hard clinical end-points, even if some indirect retrospective evidences suggest a benefit on mortality of statins in primary prevention for patients with at least one comorbidity (85). The association between statins and inflammatory activation has been more extensively studied, but for many reports describing significant decreases in inflammatory markers (42,49,88), many others failed to corroborate this finding (33,50,89). Statins have been investigated also in relation to atherosclerosis markers, with more consistent results. A 24-months course of Rosuvastatin 10 mg led to a reduction of carotid IMT in 42 patients on various HAART regimens (all on NRTI-containing regimens, 55.6% on ritonavir-boosted PI regimens, 44.4% on NNRTI containing regimens)(48), The SATURN-HIV trial randomized 147

patients, half of whom on PIs, to rosuvastatin 10 mg or placebo, reporting that 24-weeks of rosuvastatin significantly reduced monocyte activation, as measured by soluble CD14, a factor linked with faster vascular disease progression and increased cardiovascular death (26), and diminished levels of lipoprotein-associated phospholipase A_2 (Lp-PLA_2), a marker upregulated in atherosclerothic plaques and related to vascular inflammation (50); interestingly, soluble CD14 showed a trend towards a more marked reduction in patients on PIs-based regimens, while no relevant differences were noticed among different HAART regimens regarding Lp-PLA2. Moreover, a more recent analysis of the same SATURN-HIV trial reported that, after 96 weeks, Rosuvastatin 10 mg led to a significant decrease of NT-proBNP, a known predictor of CV disease (90). Pravastatin has been associated with the ability to revert lipoatrophy in patients receiving NRTI-containing regimens (45), but this finding failed to be confirmed in both patients on NRTI-containing and PI-containing regimens (41,44). In a study enrolling patients on PIs based regimens, Pravastatin 40 mg showed a tendency to increase flow-mediated vasodilation of brachial artery, a marker of decreased endothelial dysfunction (46). Finally, a 12-months course of Atorvastatin 20-40 mg in 40 patients (95% on NRTIs, 48% on PIs and 48% on NNRTIs containing regimens) ended with a reduction of atherosclerotic burden (specifically, of non-calcified plaques and high-risk lesions) as evaluated by coronary CT, even if the study failed to meet its primary end-point of a reduction of arterial inflammation measured by FDG-PET of the aorta; of note, this same study also reported a significant reduction of Lp-PLA2 values with statins (51).

Our study is, to the best of our knowledge, the largest piece of evidence confirming the lipid-lowering effectiveness of statins in patients on HAART, with all molecules tested able to provide significant reductions in total cholesterol and with rosuvastatin 10 mg providing the more convincing results when balancing safety, lipid lowering effects and consistency of supporting evidence. LDL and triglycerides were effectively reduced by almost all statins, if we exclude some non-significant results achieved by low doses of pravastatin and by fluvastatin. Besides the reduction of LDL, a well-known CV risk

factor, remarkable are the decreases of non-HDL cholesterol, which can be inferred from the reduction of total cholesterol and the modest increase of HDL, and of triglycerides. These parameters, in fact, have been increasingly identified as strong, independent predictors of adverse CV events in the general population (80,91,92) and it has been reported that their reduction may significantly reduce the burden of CV diseases (93). Based on our data, however, we can only postulate that the lipid-lowering effects of statins may lead to an improved CV outcome in HIV-positive patients; despite plausible, this hypothesis needs corroboration by mean of adequately powered and designed studies.
Pertaining to HDL, finally, as already known for non-HIV-positive patients (95), statins increased their levels inconsistently and by small margins, with only rosuvastatin 10 mg, pravastatin 10-20 mg and atorvastatin 10 mg reaching significant variations. Moreover, HDL cholesterol was the parameter more influenced by associated conditions in the meta-regression analysis, suggesting a weak relationship between its plasma variations and statin therapy.

The more critical aspect of dyslipidaemia treatment with statins in HIV-positive patients is certainly represented by interactions with HAART, which, beyond being associated with the development of unfavourable lipid profiles, is burdened by numerous drug-drug interactions, especially mediated by interference on cytochrome activity: PIs variably inhibit cytochrome (CYP) isoform 3A4 (with Ritonavir being the most potent inhibitor), while NNRTIs are inductors (Nevirapine, Efavirenz, Etravirine, Rilpivirine) (69). Moreover, simvastatin and atorvastatin are metabolized in the liver via the CYP3A4 system (96), while other statins are not (97). As a consequence, PIs may significantly increase the plasmatic concentrations of simvastatin and lovastatin, which are hence contraindicated, and of atorvastatin and rosuvatastin, which can be prescribed starting at low dosage, pending an increased risk of statin-related adverse events. Specifically, rosuvastatin has an increased risk of potential interactions with atazanavir, lopinavir and saquinavir, while atorvastatin may potentially

interact with all PIs (particularly with fosamprenavir and lopinavir). NNRTIs (specifically, Efavirenz, Etravirine and Nevirapine) may on the contrary reduce the plasmatic levels of lovastatin and simvastatin, and to a lesser extent of the other statins. Fluvastatin and pravastatin show little-to-no interactions with HAART, even if saquinavir may potentially reduce pravastatin exposure when co-administered (www.hiv-druginteractions.org). All of these pharmacokinetics mechanisms show why statin therapy is tricky in this population and cannot be approached simply based on the standard recommendations usually applied to HIV-negative patients.

In the present study, after assessment with meta-regression, PIs and NNRTIs did not show significant interactions with statins concerning their effects on total cholesterol, LDL and triglycerides concentrations. These analysis, far from considering any pharmacokinetic mechanism, confirmed that lipid-lowering therapy with statins may be effective regardless of the presence of these regimens, a finding of utmost clinical value not only in consideration of the pharmacokinetic interactions exposed above, but also because both these drug classes are associated with increased lipid levels. Even if explanation of this lack of interaction may not be univocal, a possible mechanism could be the fact that, as demonstrated in HIV-negative patients, lipid lowering effects of statins may not relevantly resent of their plasma concentration (98), as their action depends on expression and activity of hepatic uptake transporters, as organic anion transporter 1B1, which may be altered by drug-drug interactions in a scarcely predictable way (99).

A significant interaction was found with meta-regression between NRTI-sparing regimens and total cholesterol and triglycerides, with patients being prescribed with NRTIs experiencing greater lipid levels reductions. NRTIs as a pharmaceutical class have been inconsistently associated with increases in LDL and triglycerides (101); however, it has been demonstrated that regimens including tenofovir-disoproxil-fumarate may be associated with lower values of total cholesterol (74), that suspension of

this drug may lead to increases in lipid values (100,101) and that being on NRTI-sparing regimens may increase CV mortality. Even if we can suppose a critical role of tenofovir therapy on this result, we cannot infer the real weight of this effect since the studies included in our analysis didn't provide complete reports on the specific drugs prescribed for each class. Another possible explanation of this result may be that patients enrolled in the studies with the higher prevalences (≥ 65%) of NRTI-sparing regimens were treated with pravastatin, while in the other studies (14 studies, ≤ 20% of patients on NRTI-sparing regimens), rosuvastatin and atorvastatin were administered in 64.3% of cases. Furthermore it should be noted that NRTI-sparing regimens are usually administered to patients with resistant variants (often after long treatment duration) or to patients showing multiple comorbidities (including renal insufficiency, a known cardiovascular risk factor), and hence with highly controlled co-morbid conditions.

A crucial point of our analysis is represented by the generalized safety of statins in these patients, a relevant problem given the aforementioned burden of interactions. Generally, very low rates of discontinuation due to adverse events were reported for all molecules, underlining that, if conducted appropriately, statin therapy may be safe and effective in this population. Only atorvastatin 10 mg (which would not be expected to have more toxicity than higher doses) showed a high rate of discontinuation, even if no specific explanations can be provided for this finding, since, at meta-regression, no statistically significant interactions emerged, even when controlling for the different antiviral drugs. More puzzling, higher dosages of atorvastatin showed a very good safety profile, claiming for the need of further data on this topic.

From our systematic review, we found that rosuvastatin 10 mg and pravastatin 40 mg are the more extensively tested statins. Both showed a very good safety profile and were effective: rosuvastatin 10 mg reported among the higher absolute reductions of lipid concentrations and significantly augmented

HDL, while pravastatin 40 mg mildly decreased total cholesterol, LDL and triglycerides, but was unable to significantly increase HDL. Atorvastatin safety in this population is controversial and, pending more definite evidences, its prescription should be carefully evaluated on a risk/benefit ratio, while simvastatin should not typically be prescribed concomitantly to PIs due to pharmacokinetics interactions. Fluvastatin 20-40 mg appeared safe and with acceptable effectiveness; however, as it was tested only in one study, these results should be judged cautiously and other drugs should be preferred as first choice treatment.

Finally, to appraise the overall effect of statin therapy in this population, we assessed how the more prevalent treatments included in our analysis performed in HIV-positive patients as compared to the general population. With pravastatin 40 mg, total cholesterol decreased by 15.3% in HIV patients as compared to 18.3% in the general population according to a recent Phase IV study, while LDL decreased by 21.4% and 26.4% respectively (104). Rosuvastatin 10 mg reduced total cholesterol by 24.2% and LDL by 27.7% in HIV patients, as compared to 32.9% and 45.8% in the general population as reported by the Cochrane Collaboration Group (101). These figures were -20.7% (total cholesterol) and -22.0% (LDL) for Atorvastatin 10 mg in HIV-positive patients, as compared to – 27.1% and -37.1% in HIV-negative patients from a recently published meta-analysis (102). Similar results came from three studies directly comparing statins in HIV-positive vs. HIV-negative patients: Rahman et al. showed a clear trend towards a reduced LDL-lowering effect of Simvastatin 20 mg in HIV patients as compared to non—HIV controls (-36% vs. -41%, p 0.06) (53); Townsend et al. and Silverberg et al., in their retrospective analyses including various molecules and dosages, reported a significantly weaker decrease of lipid values in HIV-positive than in HIV-negative patients (30,31). These results, taken together, appear to validate the notion that dyslipidaemia and its treatment are more complex in HIV-positive patients as compared to the general population, given the peculiar mechanisms involved in

increasing lipid values and affecting therapy effectiveness, and underscore the pivotal need of a tailored approach which would be crucial to appropriately manage these patients.

LIMITATIONS.

Our study has some limitations. First the present analysis includes both randomized controlled trials and observational studies, limiting the inferential strength of our data on one side, but increasing the applicability to real world on the other side (103).

Second, it is not a patient level meta-analysis, because we would have excluded even more studies.

Finally, for some classes of statins, only few studies reported available data: however, we choose to focus on reports with statin and dose, in order to give a clear and concrete message.

CONCLUSION

Statin therapy effectively and safely lowers lipid values when administered in primary prevention to HIV-positive patients. Rosuvastatin 10 mg, supported by a consistent and vast amount of evidence, figures as the potential best fit in this population, since it achieved high reductions of total cholesterol levels, LDL and triglycerides plasma concentrations and increases of HDL values, with a very low discontinuation rate due to adverse events. HAART, despite well-characterized drug-to-drug interactions, do not appear to affect the effectiveness and safety of dose-adjusted statins, as the only significant interaction reported was an enhanced lipid-lowering effect associated with NRTIs.

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Table 1. Baseline features of enrolled patients.

	Median	Interquartile range
Age (years, min-max value)	44.1	36.3 – 56.0
Female gender	21.0	13.2 – 25.5

BMI	23.9	23.3 – 25.1
Cuacasian ethnicity	91.0	84.5 – 96.5
Men having sex with men	41.1	33.8 – 47.7
IV drug user (previous or current)	33.0	24.8 – 44.0
Hypertension	10.0	8.0 – 23.0
Smoke	46.5	45.0 – 52.3
Diabetes	0.0	0.0 – 0.0
HBV infection	3.6	2.9 – 4.2
HCV infection	21.4	17.9 – 21.9
Lenght of follow up (weeks)	12	12 – 36
Total cholesterol (mmol/l)	6.8	6.3 – 7.1
LDL cholesterol (mmol/l)	4.2	3.6 – 4.5
HDL cholesterol (mmol/l)	1.2	1.1 – 1.3
Triglycerides (mmol/l)	3.0	2.6 – 3.3

Values are expressed as percentage unless specified

BMI, body mass index; IV, intravenous; HBV, hepatitis B virus; HCV, hepatitis C virus

Table 2. HIV infection features of enrolled patients.

Values are expressed as percentage unless specified

	Median	Interquartile range
Baseline CD4+ cells (cells/mm^3)	521	423 – 552
Patients with < 50 copies/ml HIV-RNA	100.0	81.7 – 100.0
Time from HIV diagnosis (months)	106.0	74.4 – 115.0
Time on HAART (months)	65.0	62.0 – 94. 0
Patients on PI containing regimens	100.0	53.8 – 100. 0
Patients on NNRTI containing regimens	16.7	0.0 – 44.4
Patients on NRTI sparing regimens	0.0	0.0 – 4.4

HAART, highly active anti retroviral therapy; PI, protease inhibitors; NNRTI, non nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors.

FIGURE LEGENDS

Figure 1. Systematic review's profile

Figure 2. Total cholesterol reduction according to different statins and dosages; the mean reduction of

1.19 mmol/l corresponds to a decrease of 46.0 mg/dl.

Figure 3. LDL cholesterol reduction according to different statins and dosages; the mean reduction of 0.91 mmol/l corresponds to a decrease of 35.2 mg/dl.

Figure 4. Statin discontinuation due to adverse events according to different statins and dosages; discontinuation rates are expressed as events/100 person- years.

Figure 5. Metaregression of total cholesterol reduction on percentage of patients on NRTI-sparing regimens (x-axis: percentage of patients on NRTI-sparing regimens; y-axis: mean cholesterol variation in mmol/l). Area of circles is proportional to sample size.

SUPPLEMENTARY MATERIAL

Supplementary Figure 1. HDL cholesterol variation according to different statins and dosages; the mean increase of 0.07 mmol/l corresponds to a variation of 2.7 mg/dl.

Supplementary Figure 2. Triglycerides variation according to different statins and dosages; the mean variation of 0.40 mmol/l corresponds to a reduction of 35.4 mg/dl.

Supplementary Figure 3. Regression of HDL cholesterol increase on age (x-axis: age of patients; y-axis: HDL cholesterol variation in mmol/l). Area of circles is proportional to sample size.

Supplementary Figure 4. Regression of HDL cholesterol increase on percentage of patients on NNRTI-containing regimens (x-axis: percentage of patients on NNRTI containing regimens; y-axis: mean cholesterol variation in mmol/l). Area of circles is proportional to sample size.

Supplementary Figure 5. Regression of HDL cholesterol increase on percentage of patients on NRTI-sparing regimens (x-axis: percentage of patients on NRTI-sparing regimens; y-axis: mean cholesterol variation in mmol/l). Area of circles is proportional to sample size.

Supplementary Figure 6. Regression of triglycerides reduction on age (x-axis: mean age of patients; y-axis: mean triglycerides variation in mmol/l). Area of circles is proportional to sample size.

Supplementary Figure 7. Metaregression of triglycerides reduction on percentage of patients on NRTI-sparing regimens on (x-axis: percentage of patients on NRTI-sparing regimens; y-axis: mean triglycerides variation in mmol/l). Area of circles is proportional to sample size.

Supplementary Figure 8. Metaregression of triglycerides reduction on HIV infection duration (x-axis: months since HIV diagnosis; y-axis: mean triglycerides variation in mmol/l). Area of circles is proportional to sample size.

Supplementary Figure 9. Quality assessment of included studies

Supplementary Table 1. Total cholesterol and LDL reduction expressed as percentage for the different statins tested. Results are expressed as mean ± SD.

Supplementary Table 2. Metaregression analyses of main variables on total cholesterol (A), LDL (B), HDL (C), triglycerides (D) and therapy discontinuation (E).

Supplementary Table 3. Network meta-analysis for reduction after treatment of total cholesterol, LDN and HDL. (Data available on 5 RCTs with 404 patients for LDL and for 4 RCTs and 321 patients for total cholesterol).

Supplementary Table 4. Main features of included studies