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Effectiveness and safety of statins on outcomes in patients with HIV infection: a systematic review and meta-analysis

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Statins are hypolipidaemic in human immunodeficiency virus (HIV) positive individuals. However, their effect on all-cause mortality and rate of discontinuation is unclear. We conducted a systematic review to evaluate the impact of statins on all-cause mortality, discontinuation rates, and risk of adverse effects among HIV patients on highly active antiretroviral therapy (HAART). We searched four electronic databases from inception until October 2021 for trials and cohort studies evaluating the effects of statin treatment versus placebo in HIV patients. Forty-seven studies involving 91,594 patients were included. Statins were associated with significantly lower risk of discontinuation (RR, 0.701; 95% CI 0.508–0.967; $p = 0.031$). The risk of all-cause mortality (RR, 0.994; 95% CI 0.561–1.588; $p = 0.827$), any adverse effects (RR, 0.780; 95% CI 0.564–1.077; $p = 0.131$) and, diabetes mellitus (RR, 0.272; 95% CI 0.031–2.393; $p = 0.241$) with statin treatment were lower but not statistically significant compared to placebo/control. Statin treatment was associated with a trend of higher but statistically insignificant risk of myalgia (RR, 1.341; 95% CI 0.770–2.333; $p = 0.299$), elevated creatine kinase (RR, 1.101; 95% CI 0.457–2.651; $p = 0.830$) and liver enzyme activities (RR, 1.709; 95% CI 0.605–4.831; $p = 0.312$). Clinicians should consider the nocebo effect in the effective management of PLWH on statins, who present with common adverse effects such as myalgia and, elevated levels of creatine kinase and liver enzymes.

Globally, human immunodeficiency virus (HIV) infection still poses a public health threat. While the burden of HIV has steadily risen over the last decade[1], acquired immunodeficiency deficiency syndrome (AIDS)-related mortality has dropped as a result of the rapid uptake of highly active anti-retroviral therapy (HAART) over the past decade. Moreover, there is a substantial and growing burden of cardiovascular disease (CVD) among people living with HIV (PLWH), which is driven by an interaction between classical and HIV-specific factors, as well as HAART-related dyslipidaemia[2].

In PLWH, statins have a hypolipidaemic effect[3]. However, trials involving PLWH and statins have not indicated a significant reduction in mortality[4–6]. In addition, a prospective cohort research and two randomized controlled trials (RCTs) have demonstrated that adverse effects such as myalgia, elevated transaminase and creatine kinase (CK) levels, nausea, and diarrhoea are more prevalent in statin-exposed PLWH on HAART compared with those on placebo[7–9]. Data about rate of discontinuation with statins in PLWH has been conflicting. Two randomized controlled trials and one cohort study found greater discontinuation rates among statin users, whereas two randomized trials found higher discontinuation rates among placebo users[7–11].

Recent cohort studies involving PLWH did not demonstrate a statistically significant reduction in mortality between statin users and non-users[4–6]. Nonetheless, substantial limitations were observed in these cohorts; first, only 8% of PLWH were taking statin, second, the number of PLWH without statins was three times that of statin users, and third, the mortality rate was too low (8.3%) to identify a statistically significant difference.

Now, there is paucity of information about the effectiveness and safety of statin therapy for the prevention of clinical outcomes in PLWH. Therefore, we conducted a systematic review and meta-analysis to evaluate the

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efficacy and safety of statin therapy with respect to the risk of adverse events, discontinuation, and mortality in comparison to control/placebo in PLWH.

Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and more recent PRISMA-S guidelines were followed in the current meta-analysis[12,13]. No approval from an institution-related review committee was obtained for our study registered at Open Science Framework (https://doi.org/10.17605/OSF.IO/P5ETQ).

Search strategy. Relevant articles in MEDLINE (Ovid), EMBASE (Ovid), GLOBAL HEALTH (CABI), and Cochrane Library were explored from inception to October 2021 irrespective of language using the terms: ((statin) OR (HMG-CoA reductase inhibitors) OR (atorvastatin) OR (rosuvastatin) OR (fluvastatin) OR (lovastatin) OR (pitavastatin) OR (simvastatin)) AND (HIV OR AIDS OR (human AND immunodeficiency AND virus)).

Study selection. All titles and abstracts from databases search were exported to Rayyan software and identical records were deleted. The remaining records were screened by two co-authors (NNV and KOB) and any dissimilarities were resolved by consensus. Full-text articles were assessed and included in the meta-analysis if they met all the following criteria: (i) human studies, (ii) PLWH with/without HAART aged ≥ 18 years, (iii) statin treatment for primary or secondary prevention of cardiovascular event or mortality respectively, and (iv) ≥ 3-week follow up. In contrast, studies in a non-human setting and duplicate reporting were excluded.

Data extraction. Two authors (NNV and KOB) independently extracted information from each eligible study using a standardized data extraction form. We extracted data on: author's name; year of publication; sample size; study design; location of study; duration of follow-up; population and setting; baseline characteristics; type, duration and dosage of statin use; mortality from cardiovascular disease and any cause; discontinuation rates; adverse effects; and age and sex of study participants. Discrepancies in extractions were resolved by discussion. The primary endpoint was all-cause mortality. Discontinuation (owing to self-discontinuation of statin, loss to follow-up, or statin toxicity) and incidence of any adverse effects (i.e., myalgia, elevated CK and liver enzyme levels, and gastrointestinal events) and diabetes mellitus with statin treatment were secondary endpoints.

Quality and validity assessment. Two review authors (NNV and KOB) independently rated the quality of included RCTs as low, some concerns, or high risk of bias with the Cochrane Collaboration Risk of Bias tool version two (CCRBT)[14] and cohort studies were rated as good, fair, or poor using the Newcastle–Ottawa Scale[15].

Data synthesis and analysis. Median (± interquartile range) or mean (± standard deviation) was used to present continuous variables. Lipid profile values were reported in mmol/L [1 mmol/L (TC/HDL/LDL) = 38.67 mg/dL; 1 mmol/L (TG) = 88.57 mg/dL]. The risk ratios (RR) and 95% confidence intervals (CI) for all outcomes were computed using random-effects model. Statistical heterogeneity and homogeneity were estimated using I^2 statistic and Cochran Q test respectively. I^2 values of 25%, 50%, and 75% represent mild, moderate, and extensive statistical inconsistency respectively. We performed meta-regressions and subgroup analyses to determine sources of clinical heterogeneity across studies. Our subgroup analyses explored the impact of the study type (RCT, cohort studies), statin type, statin class and statin dosing intensity on treatment outcomes where applicable. The ACC/AHA classification of intensity of statin dosing was used to characterize intensity of statin dosing in the included studies[16]. Funnel plots and Begg adjusted-rank correlation and Egger regression asymmetry tests[17,18] were used to assess publication bias. To test the robustness of our results, we conducted several sensitivity analyses. All analyses were performed using Comprehensive Meta-analysis Software version 3.0 (Biostat, Englewood, NJ, USA) and R Statistical Software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org, 2020).

Results

Study selection. Our systematic literature search identified 666 articles; titles and abstracts were screened for the remaining 619 articles after removal of duplicates (Fig. 1). After full-text assessment of 80 articles, 33 studies were excluded. 47 articles met the inclusion criteria and were published from 2001–2021. Ten (21.3%) studies enrolled at least 1,000 (1,182–40,029) participants and utilized rosuvastatin 10–20 mg[8,11,19–26]. Pravastatin 40 mg[20,27–35] were evaluated in 10 studies while, 4, 3, 2 and 2 other studies utilized atorvastatin 10–40 mg[9,10,20,36], pitavastatin 2–4 mg[34,37,38], simvastatin 10–20 mg[36,39], and fluvastatin 20–40 mg[40,41] respectively (Fig. 1).

Study characteristics. Participant characteristics (Table 1) of the included studies have been summarized (see Supplementary Table S1 online) and twenty-one RCTs involving 1,482 PLWH on HAART (880 statin users vs. 602 statin non-users) were included. Majority of the studies were conducted in North America (USA = 24 and Canada = 2) while the rest in Europe (Italy = 7, France = 3, UK = 2, Germany = 1, and Denmark = 1), Asia (Thailand = 2 and China = 1), Australia (n = 3), and Uganda (n = 1). 17.0% (91,594) of females were enrolled in the 47 studies, with a median age of 46.5 years [min–max (18.0, 56.8)]. At baseline, median CD4 + T-cell count was 493×10^6 cells/L [IQR (85, 682)], mean time from HIV diagnosis was 11.5 years [IQR (0.98, 16.0)], and average HAART duration was 45.0 months [IQR (3.0, 147.0)]. The follow-up duration varied from 3.0–197 weeks (median = 12.0 weeks). Five cohort studies evaluated all-cause mortality. Fourteen RCTs and one cohort assessed discontinuation rates while twelve RCTs and one cohort reported adverse events.
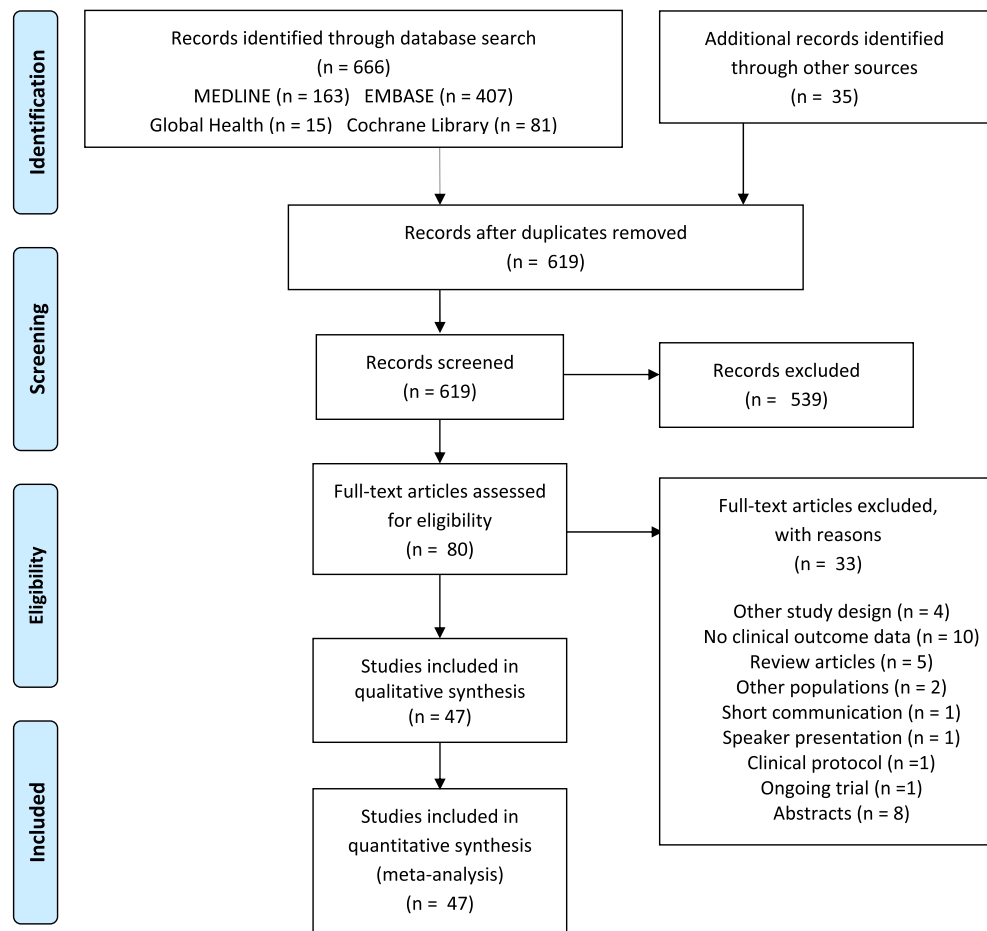
Figure 1. PRISMA flow diagram for the systematic review study selection.

	Median	Interquartile range
Age (years, min–max)	46.5	18.0–56.8
Gender Female	17.0	0–80.8
Body mass index	25.1	22.4–30.0
Caucasian ethnicity	65.5	22.5–100.0
Men having sex with men	43.8	18.2–70.0
Bisexuals	34.9	12.0–71.1
Intravenous drug user (previous or present)	13.2	0.0–45.7
Hypertension	25.9	6.7–66.0
Smoke	41.6	15.7–76.0
Diabetes Mellitus	12.0	3.8–40.0
HBV infection	6.5	3.0–36.0
HCV infection	14.6	4.7–34.9
Length of follow-up (weeks)	12.0	3–197.0
Total cholesterol (mmol/L)	5.5	3.2–7.4
HDL (mmol/L)	1.2	0.9–1.7
LDL (mmol/L)	3.4	2.4–4.3
Triglycerides (mmol/L)	2.7	1.3–9.4

Table 1. Baseline characteristics of enrolled patients.

Effects of statins on mortality in HIV patients on HAART

Study name	Risk ratio	Lower limit	Upper limit	p-Value	Risk ratio and 95% CI
Moore et al (2011)	0.490	0.229	1.049	0.066	
Rasmussen et al (2013)	1.019	0.617	1.685	0.940	
Lang et al (2015)	1.017	0.450	2.299	0.967	
Phan et al (2020)	0.505	0.162	1.571	0.238	
Bedimo et al (2021)	1.655	1.508	1.817	0.000	
	0.944	0.561	1.588	0.827	
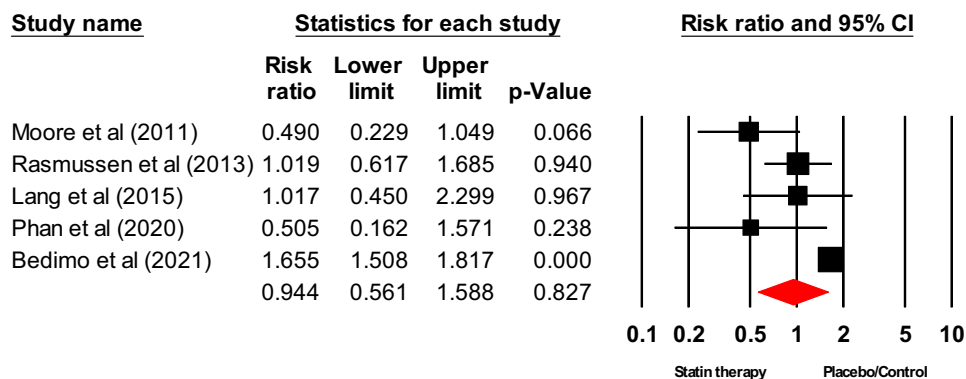
Random effect meta-analysis

Figure 2. Forest plot comparing the impact of statins versus placebo on all-cause mortality in HIV-infected patients on HAART.

Effects of statins on discontinuation of treatment in HIV patients on HAART

Group by / Subgroup within study	Author & Year	Study Type	Risk ratio	Lower limit	Upper limit	p-Value	Risk ratio and 95% CI
Cohort study	Calzaetal2014	Cohort study	1.150	0.170	7.794	0.886	
Cohort study			1.150	0.170	7.794	0.886	
RCT	Moyleetal2001	RCT	0.267	0.033	2.124	0.212	
RCT	Mallonetal2006	RCT	5.294	0.273	102.486	0.270	
RCT	Bonnetetal2007	RCT	3.846	0.207	71.477	0.366	
RCT	Maccallanetal2008	RCT	1.182	0.119	11.724	0.887	
RCT	Calmyetal2010	RCT	4.231	0.226	79.096	0.334	
RCT	Bakeretal2012	RCT	0.778	0.371	1.631	0.506	
RCT	Grandietal2014	RCT	3.143	0.135	72.922	0.475	
RCT	Eckardetal2014	RCT	1.042	0.352	3.081	0.941	
RCT	Funderburgetal2015	RCT	0.391	0.162	0.942	0.036	
RCT	Loetal2015	RCT	2.211	0.217	22.468	0.503	
RCT	Nouetal2016	RCT	2.211	0.217	22.468	0.503	
RCT	Longeneckeretal2016	RCT	0.603	0.309	1.177	0.138	
RCT	Hilemanetal2017	RCT	0.493	0.239	1.018	0.056	
RCT			0.691	0.498	0.958	0.026	
Overall			0.701	0.508	0.967	0.031	

Random effect meta-analysis

Figure 3. Forest plot comparing the impact of statins versus placebo on discontinuation of treatment in HIV-infected patients on HAART.
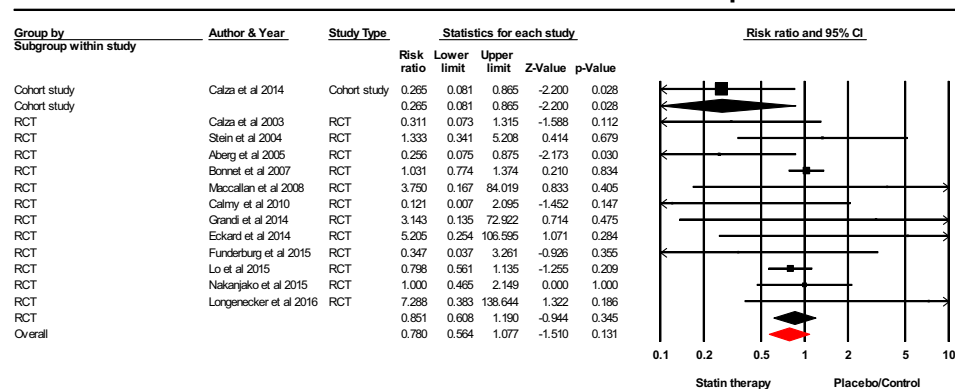
Effect of statin treatment on all-cause mortality in HIV-infected patients. Statins were comparable to placebo/control in reducing all-cause mortality in PLWH with/without HAART (RR; 0.994; 95% CI 0.561–1.588; $p = 0.827$) (Fig. 2).

Effect of statins on discontinuation rates among patients with HIV. Statins in HAART exposed or unexposed PLWH is associated with lower risk of discontinuation (RR; 0.701; 95% CI 0.508–0.967; $p = 0.031$) compared with placebo/control in these patients–control group (Fig. 3).

Effect of statin treatment on incidence of adverse events in HIV-infected patients. Statin therapy was not significantly associated with lower incidence of any adverse effects (RR; 0.780; 95% CI 0.564–1.077; $p = 0.131$), gastrointestinal adverse effects (RR; 0.830; 95% CI 0.493–1.398; $p = 0.484$), and diabetes mellitus (RR; 0.272; 95% CI 0.031–2.393; $p = 0.241$) compared to placebo/control. There was a non-significant increase in the risk of myalgia (RR; 1.341; 95% CI; 0.770–2.333; $p = 0.299$) and elevated liver enzymes (RR; 1.709; 95% CI; 0.605–4.831; $p = 0.312$) with statins compared to placebo/control (Fig. 4a-f).
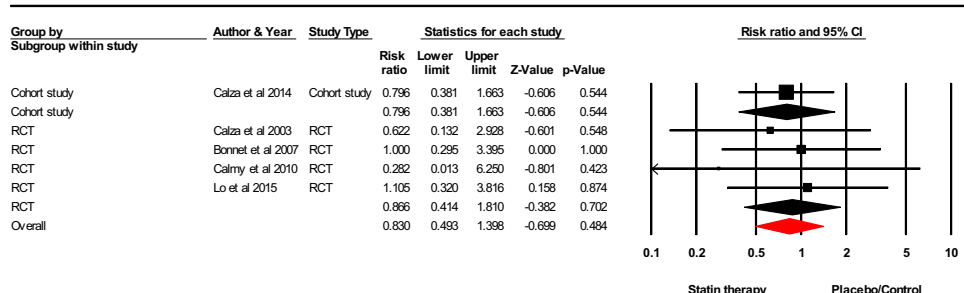
Pooled results from 5 RCTs with 404 patients on statins or placebo/standard treatment demonstrated a non-significant lower risk of elevated CK (RR; 0.891; 95% CI; 0.342–2.319; $p = 0.813$) while the overall pooled results

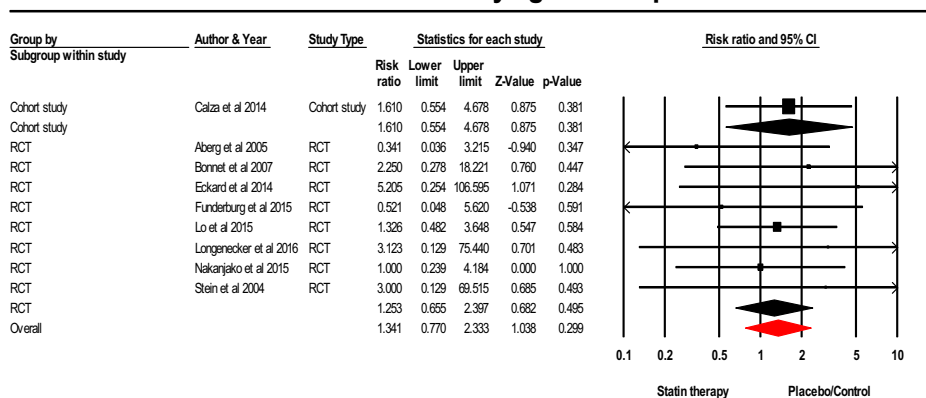## a Effects of statins on incidence of adverse effects in HIV patients on HAART

Group by Subgroup within study	Author & Year	Study Type	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Risk ratio and 95% CI
Cohort study	Calza et al 2014	Cohort study	0.265	0.081	0.865	-2.200	0.028	
Cohort study			0.265	0.081	0.865	-2.200	0.028	
RCT	Calza et al 2003	RCT	0.311	0.073	1.315	-1.588	0.112	
RCT	Stein et al 2004	RCT	1.333	0.341	5.208	0.414	0.679	
RCT	Aberg et al 2005	RCT	0.256	0.075	0.875	-2.173	0.030	
RCT	Bonnet et al 2007	RCT	1.031	0.774	1.374	0.210	0.834	
RCT	Maccallan et al 2008	RCT	3.750	0.167	84.019	0.833	0.405	
RCT	Calmy et al 2010	RCT	0.121	0.007	2.095	-1.452	0.147	
RCT	Grandi et al 2014	RCT	3.143	0.135	72.922	0.714	0.475	
RCT	Eckard et al 2014	RCT	5.205	0.254	106.595	1.071	0.284	
RCT	Funderburg et al 2015	RCT	0.347	0.037	3.261	-0.926	0.355	
RCT	Lo et al 2015	RCT	0.798	0.561	1.135	-1.255	0.209	
RCT	Nakanjako et al 2015	RCT	1.000	0.465	2.149	0.000	1.000	
RCT	Longenecker et al 2016	RCT	7.288	0.383	138.644	1.322	0.186	
RCT			0.851	0.608	1.190	-0.944	0.345	
Overall			0.780	0.564	1.077	-1.510	0.131	

Random effect meta-analysis

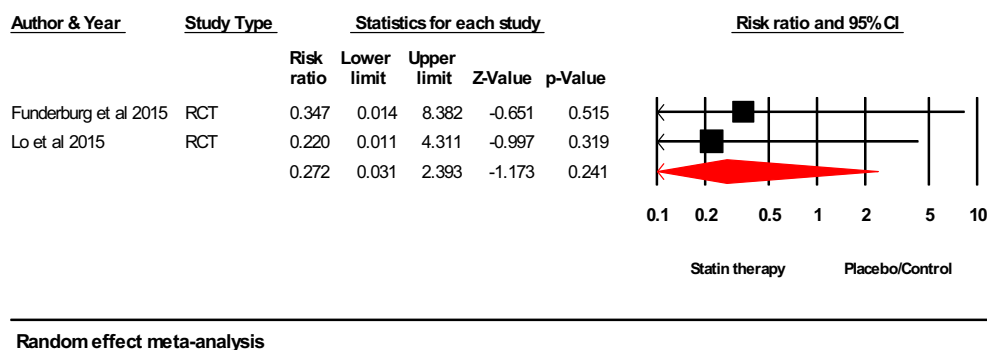## b Effects of statins on incidence of gastrointestinal adverse effects in HIV patients on HAART

Group by Subgroup within study	Author & Year	Study Type	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Risk ratio and 95% CI
Cohort study	Calza et al 2014	Cohort study	0.796	0.381	1.663	-0.606	0.544	
Cohort study			0.796	0.381	1.663	-0.606	0.544	
RCT	Calza et al 2003	RCT	0.622	0.132	2.928	-0.601	0.548	
RCT	Bonnet et al 2007	RCT	1.000	0.295	3.395	0.000	1.000	
RCT	Calmy et al 2010	RCT	0.282	0.013	6.250	-0.801	0.423	
RCT	Lo et al 2015	RCT	1.105	0.320	3.816	0.158	0.874	
RCT			0.866	0.414	1.810	-0.382	0.702	
Overall			0.830	0.493	1.398	-0.699	0.484	

Random effect meta-analysis

c Effects of statins on incidence of myalgia in HIV patients on HAART

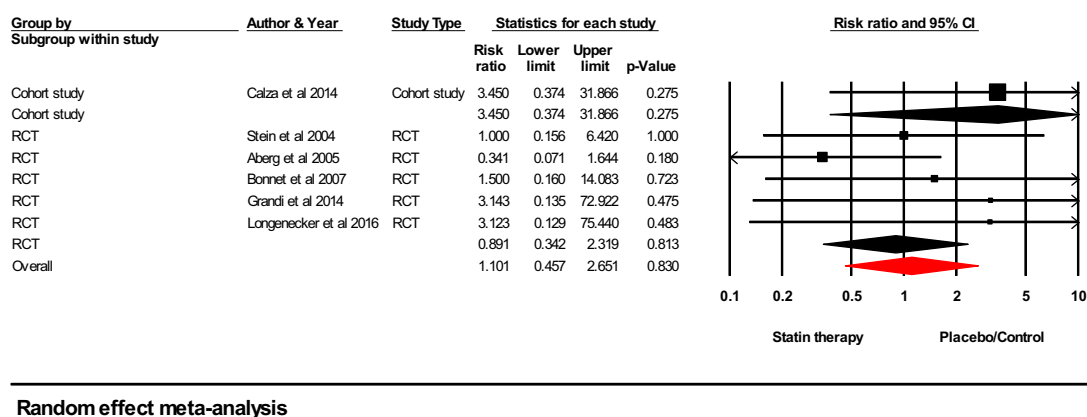| Group by Subgroup within study	Author & Year	Study Type	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Risk ratio and 95% CI
Cohort study	Calza et al 2014	Cohort study	1.610	0.554	4.678	0.875	0.381	
Cohort study			1.610	0.554	4.678	0.875	0.381	
RCT	Aberg et al 2005	RCT	0.341	0.036	3.215	-0.940	0.347	
RCT	Bonnet et al 2007	RCT	2.250	0.278	18.221	0.760	0.447	
RCT	Eckard et al 2014	RCT	5.205	0.254	106.595	1.071	0.284	
RCT	Funderburg et al 2015	RCT	0.521	0.048	5.620	-0.538	0.591	
RCT	Lo et al 2015	RCT	1.326	0.482	3.648	0.547	0.584	
RCT	Longenecker et al 2016	RCT	3.123	0.129	75.440	0.701	0.483	
RCT	Nakanjako et al 2015	RCT	1.000	0.239	4.184	0.000	1.000	
RCT	Stein et al 2004	RCT	3.000	0.129	69.515	0.685	0.493	
RCT			1.253	0.655	2.397	0.682	0.495	
Overall			1.341	0.770	2.333	1.038	0.299	

Random effect meta-analysis

Figure 4. (**a**) Forest plot comparing the impact of statins versus placebo on incidence of any adverse effects in HIV-infected patients on HAART. (**b**) Forest plot comparing the impact of statins versus placebo on incidence of gastrointestinal adverse effects in HIV-infected patients on HAART. (**C**) Forest plot comparing the impact of statins versus placebo on incidence of malgia in HIV-infected patients on HAART. (**d**) Forest plot comparing the impact of statins versus placebo on incidence of diabetes mellitus in HIV-infected patients on HAART. (**e**) Forest plot comparing the impact of statins versus placebo on incidence of creatine kinase elevation in HIV-infected patients on HAART. (**f**) Forest plot comparing the impact of statins versus placebo on incidence of elevated liver enzymes in HIV-infected patients on HAART.

d

Effects of statins on incidence of diabetes mellitus in HIV patients on HAART

Author & Year	Study Type	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Funderburg et al 2015	RCT	0.347	0.014	8.382	-0.651	0.515
Lo et al 2015	RCT	0.220	0.011	4.311	-0.997	0.319
		0.272	0.031	2.393	-1.173	0.241

Random effect meta-analysis

e

Effects of statins on creatine kinase elevation in HIV patients on HAART

Group by Subgroup within study	Author & Year	Study Type	Risk ratio	Lower limit	Upper limit	p-Value
Cohort study	Calza et al 2014	Cohort study	3.450	0.374	31.866	0.275
Cohort study			3.450	0.374	31.866	0.275
RCT	Stein et al 2004	RCT	1.000	0.156	6.420	1.000
RCT	Aberg et al 2005	RCT	0.341	0.071	1.644	0.180
RCT	Bonnet et al 2007	RCT	1.500	0.160	14.083	0.723
RCT	Grandi et al 2014	RCT	3.143	0.135	72.922	0.475
RCT	Longenecker et al 2016	RCT	3.123	0.129	75.440	0.483
RCT			0.891	0.342	2.319	0.813
Overall			1.101	0.457	2.651	0.830

Random effect meta-analysis

f

Effects of statins on elevated liver enzymes in HIV patients on HAART

Group by Subgroup within study	Author & Year	Study Type	Risk ratio	Lower limit	Upper limit	p-Value
Cohort study	Calza et al 2014	Cohort study	1.725	0.303	9.811	0.539
Cohort study			1.725	0.303	9.811	0.539
RCT	Stein et al 2004	RCT	1.000	0.067	14.904	1.000
RCT	Maccallan et al 2008	RCT	3.750	0.167	84.019	0.405
RCT	Lo et al 2015	RCT	1.658	0.310	8.879	0.555
RCT			1.701	0.465	6.214	0.422
Overall			1.709	0.605	4.831	0.312

Random effect meta-analysis

Figure 4. (continued)

for 490 statin-treated patients versus non-users among non-randomized studies showed an increase in risk of elevated CK (RR; 1.101; 95% CI; 0.457–2.651; $p = 0.830$) but not statistically significant (Fig. 4a-f).

Risk of bias. About 54% of the cohort studies were of good quality while about 35% were of fair quality (see Supplementary Table S2 online). About 14.3% of the RCTs had a "low" risk of bias, 61.9% "some concerns" risk of bias and 23.8% "high" risk of bias (see Supplementary Fig. S1**a,b** online).

Meta-regressions and sensitivity analyses. Baseline characteristics (see Supplementary Table S3 online) of HAART-treated PLWH varied widely across included studies (see Supplementary Table S4 online). Also, we combined cohort studies and RCTs in our meta-analysis, but our results indicated low heterogeneity ($I^2 < 50\%$) for most study outcomes except all-cause mortality which showed high heterogeneity ($I^2 > 70\%$) with fixed effect meta-analysis. The impact of potential heterogeneity was minimized by using a DerSimonian-Laird random-effect model in analysis. Where applicable, we conducted mixed effect meta-regressions to explore the impact of patients' baseline characteristics on treatment effects of statins versus placebo/control. The meta-regression models (see Supplementary Table S3 online) confirmed some wide variations in baseline characteristics (see Supplementary Table S4 online). After controlling for study design, year of publication and all other baseline factors, female sex (RR; 1.36; 95%CI; 1.00–1.85; $p = 0.049$), HDL-c (RR; 2.0×10^{-5}; 95%CI; 3.8×10^{-10}-1.06; $p = 0.051$) and HIV-RNA copies (RR; 1.00; 95%CI; 1.00–1.01; $p = 0.047$) remained significantly associated with incidence of adverse effects of statin treatment versus placebo/control (see Supplementary Table S3 online). Mixed effect meta-regression did not show any significant association between baseline factors and statin discontinuation rates (see Supplementary Table S4 online).

Sensitivity analyses did not demonstrate any changes in effect estimates for all study outcomes (adverse events, I^2: 36.98%; discontinuation rate, I^2: 0.00%; all-cause mortality, I^2: 77.74%) (see Supplementary Fig. S2-S8 online). In subgroup analyses, rosuvastatin was associated with reduced risk of statin discontinuation compared to placebo/control (RR; 0.633; 95% CI; 0.410–0.979; $p = 0.040$); pravastatin was associated with a non-significant lower risk of statin discontinuation (RR; 0.719; 95% CI; 0.436–1.187; $p = 0.197$). Atorvastatin was associated with higher risk of statin discontinuation but statistically non-significant compared to placebo/control (RR; 2.21; 95% CI; 0.429–11.392; $p = 0.343$). In addition, we found that moderate-intensity dosing was associated with lower risk of discontinuation compared to placebo (RR; 0.684; 95% CI; 0.478–0.978; $p = 0.037$) (see Supplementary Fig. S9-S11 online; Supplementary Fig. S12-S14 online).

Publication bias. Publication bias was assessed for all outcomes using funnel plots and Begg adjusted-rank correlation[17] and Egger regression asymmetry tests[18]. We found no significant publication bias for most of the study outcomes except for discontinuation rate.

GRADE assessment of quality of evidence. The quality of evidence for each of the following outcomes: all-cause mortality, treatment discontinuation, and incidence of adverse effects, gastrointestinal adverse effects, myalgia, diabetes mellitus, elevated CK, and elevated liver enzymes was assessed using the GRADEpro online tool. Certainties of the absolute effects of statins on the assessed outcomes were moderate to high indicating high quality of evidence (See Supplemental Table S5).

Discussion

We compared the effects of statins on all-cause mortality, discontinuation rates, and incidence of adverse effects with placebo/control in HAART-exposed PLWH using a meta-analysis of 21 RCTs and 26 cohort studies involving 91,594 individuals followed up for a median of 3 months (IQR, 0.8–49.3 months). Compared to placebo/control, statins were associated with significantly lower discontinuation rates. In addition, statin did not lower the risk of myalgia or liver enzyme elevations in PLWH on HAART. Statin did not significantly reduce all-cause mortality or the incidence of adverse events, diabetes mellitus, increased CK elevation, or gastrointestinal side effects in PLWH with prior HAART exposure.

In a recent meta-analysis of 9 cohort studies comprising 73,256 people, Li and colleagues discovered that statins were associated with a 44% reduction in all-cause mortality[42]. Moreover, a meta-analysis of 7 cohort studies in PLWH with/without HAART showed that statins were linked to a 33% reduction in all-cause mortality[43]. The larger sample sizes and the proportion of patients on statins in the studies included in prior meta-analyses may account for the statistically significant reduction in mortality compared with placebo. However, we found a modest reduction in all-cause mortality, which was not statistically significant. This study supports recent findings by Phan and colleagues who demonstrated no significant difference in all-cause mortality between statin users and non-users (HR; 0.74; 95% CI; 0.17–3.29; $p = 0.70$)[5]. According to Lang et al., statins have the same effect on death from all causes as a placebo (HR; 0.86; 95% CI; 0.34–2.19)[6].

Our meta-analysis on all-cause mortality involved data from 5 cohort studies of PLWH on HAART with follow-up durations from 38–156 months. Statins did not significantly lower all-cause mortality among PLWH in our pooled results, which is consistent with earlier research by Rasmussen et al.[44], Lang et al.[6], and Phan et al.[5]. Conversely, our results did not support the findings of Moore et al. and Bedimo et al.[45,46]. The longer follow-up duration and larger placebo groupsize observed in Moore et al.'s study may explain the significant reduction in all-cause mortality seen with statin treatment compared with control/standard treatment. Moreover, Bedimo et al.'s[46] results do not corroborate our findings plausibly due to their longer follow-up, older HIV-infected patients, and fewer female patients.

The discontinuation rate is an important factor in the assessment of a drug's effectiveness in routine practice[47]. Our meta-analysis of 13 RCTs (n = 878) and one cohort study (n = 86) revealed that the discontinuation rate among PLWH taking statins was significantly lower than that of non-statin users. This may be due to the fact that the subjects included in our study were younger and that some of them (~ 50%) had never used protease inhibitors. Use of protease inhibitors and advanced age are known risk factors for statin toxicity and consequently statin-related side events. In the studies that were included, self-discontinuation and loss to follow-up were the most common reasons for stopping statin/control medication[8–11,25,48,49] while statin-related adverse effects such as elevated CK and liver enzymes levels and myopathy were less common reasons[7,8,11,25,33].

Our study does not support findings of Gili et al.'s meta-analysis of 736 HAART-exposed PLWH[26] that found a higher incidence of statin discontinuation (MD, 0.12 per 100 person-years; 95% CI 0.05–0.20). Patients had HIV infection for 8.8 years; were exposed to HAART for about 5.4 years and commonly used 10 mg atorvastatin as statin treatment. Patients included in Gili et al.'s meta-analysis had few differences from ours in terms of patients' characteristics which includes; more female subjects (median, 21.0% vs. 17.0%; IQR: 13.2–25.5% vs. 0–80.8%) and protease inhibitor use (76.5% vs. 50.1%), lower BMI (median 23.9 vs. 25.1; IQR: 23.3–25.1 vs. 22.4–30.0), and 10 mg atorvastatin use (vs. 10 mg rosuvastatin and 20–40 mg pravastatin use). Low BMI, female sex, statin class, and protease inhibitors have been identified as risk factors of statin toxicity[50]. Protease inhibitors block the CYP34A pathway and as a result produce high and toxic plasma levels of lipophilic statins like atorvastatin. Lipophilic statins are more likely to cause myopathy because they more readily permeate into skeletal muscle[50]. This could explain why the risk of statin discontinuation in this study, was lower than with control or placebo group.

In contrast, our data support a prior meta-analysis by Riaz et al. that included 17,770 patients (OR. 0.99; 95% CI 0.93–1.06) and found that patients receiving placebo had higher but non-significant discontinuation rates than those receiving statins (13.9% (n = 8,898) vs. 13.3% (n = 8872))[35]. Our pooled results provide additional support for findings from another meta-analysis of 19 RCTs involving 71,344 patients exposed to statins and those exposed to a placebo, which found no association between statin treatment and a lower risk of discontinuation (RR; 0.95; 95% CI: 0.75–1.21)[51]. Additionally, our study supports the findings of previous RCTs[8,25,48,49] that showed statin-unexposed PLWH had greater discontinuation rates than statin-exposed PLWH.

Our subgroup analyses revealed that rosuvastatin was significantly associated with lower risk of statin discontinuation relative to placebo (RR; 0.633; 95% CI: 0.410–0.979; $p = 0.040$) in PLWH on HAART. This could be explained by the fact that pravastatin (hydrophilic) is solely metabolized by OAT 1, whereas rosuvastatin (hydrophilic) is a substrate to both organic anion transporting polypeptides 1 (OAT 1) and cytochrome P450[52]. Compared to lipophilic, hydrophilic statins are less likely to cause myopathy because they less readily permeate into skeletal muscles. Moreover, protease inhibitors are able to produce toxic plasma levels of lipophilic statins like atorvastatin, which result in higher rate of statin discontinuation[50]. Our subgroup analysis focusing on the impact of statin intensity demonstrated a 31.6% lower risk of discontinuation with moderate-dose statin versus placebo (RR; 0.684; 95% CI: 0.478–0.978; $p = 0.037$). On the contrary, Gili et al. found higher risk of statin discontinuation with moderate-dose rosuvastatin (MD; 0.44; 95% CI: 0.22–0.65; $p < 0.0001$)[26]. Additionally, our research does not corroborate the findings of Vinogradova et al.'s study, which revealed that statin type and dose are not important determinants of discontinuation[53]. Gili and colleagues defined statin discontinuation as cessation of treatment based on statin-related adverse effects. In contrast, we took into account side effects related to statins, self-withdrawal, and loss to follow-up.

Statin-related adverse events in PLWH on HAART are a major reason for statin discontinuation. The high prevalence of myalgia among PLWH may be attributed to statin class, statin dose, protease inhibitors, concurrent use of medications such as fibrates and niacin, advanced age (> 75 years), female sex, low BMI, alcoholism, and vitamin D deficiency. We found no significant association between statin treatment and increased risk of myalgia and elevated levels of liver enzymes and CK in PLWH. Also, no significant association of statins with risk of any adverse effects, gastrointestinal symptoms, and diabetes mellitus was found. Our findings are consistent with results from Calza et al.'s study, which found that myalgia and increased CK activity are prevalent in HAART-treated PLWH on statins but are not significantly associated with statins[7]. Similarly, a meta-analysis of eighteen studies (n = 106,321) found equal rates of myopathy between statins and placebo groups of PLWH (OR; 1.2; 95% CI = 0.88–1.62)[35]. However, a recent meta-analysis by Cai et al. found a significantly elevated incidence of myalgia (21 RCTs, n = 65, 304) and liver dysfunction (21 trials, n = 54,803) among the HIV-uninfected persons with or without statins[54]. This disparity could be explained by the fact that majority of Cai et al.'s pooled studies that indicated liver dysfunction included patients on 10–80 mg atorvastatin. Statin-induced hepatotoxicity can be caused by: i) inhibition of the mevalonate pathway; ii) changes in lipid composition of the hepatocyte membranes; and iii) lipophilicity with high oral daily dose of statin[50].

Statins, particularly high-dose statin and rosuvastatin, increases the risk of developing new-onset diabetes mellitus[50]. Atorvastatin lowers the concentrations of glucose transporter 4 and caveolin-1 in skeletal muscle[50,52]. The SATURN (Stopping Atherosclerosis and Treating Unhealthy bone with Rosuvastasin in HIV) trial and HIV Outpatient (HOP) cohort study both found significant associations between of statin use and diabetes mellitus[55,56]. In contrast, a cohort study of 6,195 patients conducted by Spagnuolo et al. complements our findings by demonstrating that statin use was associated with a non statistically significant increase in incidence of diabetes mellitus (HR: 1.21; 95% CI: 0.71–2.07; p = 0.47)[57]. Only two trials[9,11] of the 47 included studies reported incidence of diabetes mellitus among HIV patients on statin treatment.

Strength and limitations

To the best of our knowledge, we are the first meta-analysis to investigate the effects of statin therapy on rates of discontinuation and adverse events among PLWH. Using the Newcastle–Ottawa scale, all the studies included in our meta-analysis on all-cause mortality were of good quality.

Our meta-analysis was without limitations. First, no identified RCTs reported all-cause mortality, and our meta-analysis comprised few cohort studies. Second, cardiovascular mortality was not pooled since only one trial reported it. Thirdly, dosage, type, and follow-up varied considerably among the included RCTs. However, our meta-regressions and subgroup analyses investigated the influence of sources of heterogeneity on treatment outcomes. Finally, only English-language data were included, resulting in the likely omission of trials published in other languages. However, our assessment of publication bias did not reveal significant bias for the majority of the study outcomes.

Conclusions

The discontinuation rate of statin-treated PLWH is considerably lower than placebo/control patients. Among PLWH, statin treatment did not significantly lower mortality from all causes. Clinicians should consider the nocebo effect when treating PLWH who are taking statins and have common adverse effects such as myalgia and, elevated levels of CK and liver enzymes.

Data availability

Data can be obtained from the corresponding author on reasonable scientific request. Requests to access the datasets should be directed to Njeodo Vigny, N.Vigny64@gmail.com.

References

1. UNAIDS. Global: HIV/AIDS estimates. https://www.unaids.org/en/resources/fact-sheet. Accessed on 28 May 2020.
2. Feinstein, M. J. *et al.* Characteristics, prevention, and management of cardiovascular disease in people living with HIV-a scientific statement from the american heart association. *Circ.* **140**, e98–e124 (2019).
3. Bernal, E. *et al.* Statins in HIV-infected patients: potential beneficial effects and clinical use. *AIDS. Rev.* **19**, 59–71 (2017).
4. Ou, H. T. *et al.* Intensive statin regimens for reducing risk of cardiovascular diseases among human immunodeficiency virus-infected population: a nation-wide longitudinal cohort study 2000–2011. *Int. J. Cardiol.* **230**, 592–598 (2017).
5. Phan, B. A. *et al.* Association between statin use, atherosclerosis, and mortality in HIV-infected adults. *PLoS ONE* **15**, 1–11 (2020).
6. Lang, S. *et al.* Is impact of statin therapy on all-cause mortality different in HIV-infected individuals compared to general population? Results from the FHDH-ANRS CO4 cohort. *PLoS ONE* **10**, 1–9 (2015).
7. Calza, L. *et al.* Tenofovir/ emtricitabine/efavirenz plus rosuvastatin decrease serum levels of inflammatory markers more than antiretroviral drugs alone in antiretroviral therapy-naive HIV-infected patients. *HIV Clin. Trials.* **15**, 1–3 (2014).
8. Longenecker, C. T. *et al.* Rosuvastatin slows progression of subclinical atherosclerosis in patients with treated HIV infection. *AIDS* **30**, 2195 (2016).
9. Lo, J. *et al.* Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: A randomized, double-blind, placebo-controlled trial. *Lancet HIV.* **2**, e52-63 (2015).
10. Nou, E. *et al.* Serum oxidized low-density lipoprotein decreases in response to statin therapy and relates independently to reductions in coronary plaque in patients with HIV. *AIDS* **30**, 583–590 (2016).
11. Funderburg *et al.* Rosuvastatin reduces vascular inflammation and T cell and monocyte activation in HIV-infected subjects on antiretroviral therapy. *J. Acqui. Immune Defic. Syndr.* **68**, 396 (2015).
12. Page, M.J., *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* **372** (2021).
13. Rethlefsen, M. L. *et al.* PRISMA-S: An extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst. Rev.* **10**, 1–9 (2021).
14. Higgins, J.P.T., *et al.* Assessing risk of bias in a randomized trial. Cochrane handbook for systematic reviews of interventions, 2019.
15. Zeng, X. *et al.* The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J. Evid. Based Med.* **8**, 2–10 (2015).
16. Grundy, S. M. *et al.* 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ ASPC/NLA/PCNA guideline on the management of blood cholesterol: Executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *JACC.* **73**, 3168–3209 (2019).
17. Begg, C. B. *et al.* Operating characteristics of a rank correlation test for publication bias. *Biom.* **50**, 1088–1101 (1994).
18. Egger, M. *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634 (1991).
19. Johns, K. W. *et al.* Are HIV positive patients resistant to statin therapy?. *Lipids Health Dis.* **6**, 1–5 (2007).
20. Calza, L. *et al.* Statin therapy decreases serum levels of high-sensitivity C-reactive protein and tumor necrosis factor-α in HIV-infected patients treated with ritonavir-boosted protease inhibitors. *HIV Clin. Trials.* **13**, 153–161 (2012).
21. Calza, L. *et al.* Tenofovir/emtricitabine/efavirenz plus rosuvastatin decrease serum levels of inflammatory markers more than antiretroviral drugs alone in antiretroviral therapy-naive HIV-infected patients. *HIV Clin. Trials.* **15**, 1–3 (2014).
22. Saeedi, R. *et al.* Lipid lowering efficacy and safety of ezetimibe combined with rosuvastatin compared with titrating rosuvastatin monotherapy in HIV-positive patients. *Lipids Health Dis.* **14**, 1–8 (2015).
23. Calza, L. *et al.* Rosuvastatin decreases serum inflammatory markers and slows atherosclerosis progression rate in treated HIV-infected patients with metabolic syndrome. *Infect. Dis.* **53**, 81–88 (2021).
24. Hearps, A. C. *et al.* Effect of rosuvastatin therapy on biomarkers of inflammation and immune activation in people with human immunodeficiency virus at intermediate cardiovascular risk. *J. Infect. Dis.* **224**, 667–672 (2021).
25. Eckard, A. R. *et al.* Effect of 24 weeks of statin therapy on systemic and vascular inflammation in HIV-infected subjects receiving antiretroviral therapy. *J. Infect. Dis.* **209**, 1156–1164 (2014).
26. Gili, S. *et al.* Comparative safety and efficacy of statins for primary prevention in human immunodeficiency virus-positive patients: A systematic review and meta-analysis. *Eur. Heart J.* **37**, 3600–3609 (2016).
27. Moyle, G. J. *et al.* Dietary advice with or without pravastatin for the management of hypercholesterolaemia associated with protease inhibitor therapy. *AIDS* **15**, 1503–1508 (2001).
28. Stein, J. H. *et al.* Effects of pravastatin on lipoproteins and endothelial function in patients receiving human immunodeficiency virus protease inhibitors. *Am. Heart J.* **147**, 713 (2004).
29. Aberg, J. A. *et al.* A randomized trial of the efficacy and safety of fenofibrate versus pravastatin in HIV-infected subjects with lipid abnormalities: AIDS clinical trials group study 5087. *AIDS Res. Hum. Retroviruses.* **21**, 757–767 (2005).
30. Mallon, P. W. *et al.* Effect of pravastatin on body composition and markers of cardiovascular disease in HIV-infected men–a randomized, placebo-controlled study. *AIDS* **20**, 1003–1010 (2006).
31. Bonnet, F. *et al.* Pravastatin in HIV-infected patients treated with protease inhibitors: A placebo-controlled randomized study. *HIV Clin. Trials.* **8**, 53–60 (2007).
32. Macallan, D. C. *et al.* Treatment of altered body composition in HIV-associated lipodystrophy: Comparison of rosiglitazone, pravastatin, and recombinant human growth hormone. *HIV Clin. Trials.* **9**, 254–268 (2008).
33. Grandi, A. M. *et al.* Dyslipidemia in HIV-positive patients: A randomized, controlled, prospective study on ezetimibe+fenofibrate versus pravastatin monotherapy. *J. Int. AIDS Soc.* **17**, 19004 (2014).
34. Toribio, M. *et al.* Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in INTREPID: A randomized trial in HIV. *AIDS* **31**, 797 (2017).
35. Riaz, H. *et al.* Meta-analysis of placebo-controlled randomized controlled trials on the prevalence of statin intolerance. *Am. J. Cardiol.* **120**, 774–781 (2017).
36. Boettiger, D. C. *et al.* Maintenance of statin therapy among people living with HIV. *AIDS* **35**, 567–574 (2021).

37. Wongprikorn, A. *et al.* Effects of pitavastatin on lipid profiles in HIV-infected patients with dyslipidemia and receiving atazanavir/ritonavir: A randomized, double-blind, crossover study. *PLoS ONE* **11**, e0157531 (2016).
38. deFilippi, C. *et al.* Differential plasma protein regulation and statin effects in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients utilizing a proteomics approach. *J. Infect. Dis.* **222**, 929–939 (2020).
39. Rahman, A. P. *et al.* Safety and efficacy of simvastatin for the treatment of dyslipidemia in human immunodeficiency virus-infected patients receiving efavirenz-based highly active antiretroviral therapy. *Pharmacotherapy J. Hum. Pharmacol. Drug Ther.* **28**, 913–9 (2008).
40. Calza, L. *et al.* Statins and fibrates for the treatment of hyperlipidaemia in HIV-infected patients receiving HAART. *AIDS* **17**, 851–859 (2003).
41. Benesic, A. *et al.* Lipid lowering therapy with fluvastatin and pravastatin in patients with HIV infection and antiretroviral therapy: Comparison of efficacy and interaction with indinavir. *Infect.* **32**, 229–233 (2004).
42. Li, Y., et al. Influence of statin therapy on the incidence of cardiovascular events, cancer, and all-cause mortality in people living with HIV: A meta-analysis. *Front. Med.* 8 (2021).
43. Uthman, O. A. *et al.* Statin use and all-cause mortality in people living with HIV: A systematic review and meta-analysis. *BMC Infect. Dis.* **18**, 1–8 (2018).
44. Rasmussen, L. D. *et al.* Statin therapy and mortality in HIV-infected individuals; a danish nationwide population-based cohort study. *PLoS ONE* **8**, e52828 (2013).
45. Moore, R. D. *et al.* Association between use of HMG CoA reductase inhibitors and mortality in HIV-infected patients. *PLoS ONE* **6**, e21843 (2011).
46. Bedimo, R. J. *et al.* Statin exposure and risk of cancer in people with and without HIV infection. *AIDS* **35**, 325–334 (2021).
47. Dekkers, C. C. *et al.* Overcoming obstacles in lipid-lowering therapy in patients with HIV-a systematic review of current evidence. *AIDS Rev.* **20**, 205–219 (2018).
48. Hileman, C. O. *et al.* Baseline vitamin D deficiency decreases the effectiveness of statins in HIV-infected adults on antiretroviral therapy. *J. Acqui. Immune Defic. Syndr.* **74**, 539 (2017).
49. Calmy, A. *et al.* No significant effect of uridine or pravastatin treatment for HIV lipoatrophy in men who have ceased thymidine analogue nucleoside reverse transcriptase inhibitor therapy: A randomized trial. *HIV Med.* **11**, 493–501 (2010).
50. Ward, N. C. *et al.* Statin toxicity: Mechanistic insights and clinical implications. *Circ. Res.* **124**, 328–350 (2019).
51. Chou, R. *et al.* Statins for prevention of cardiovascular disease in adults: Evidence report and systematic review for the US preventive services task force. *JAMA* **316**, 2008–2024 (2016).
52. Newman, C. B. *et al.* Statin safety and associated adverse events: A scientific statement from the american heart association. *Arterioscler. Thromb. Vasc. Biol.* **39**, e38-81 (2019).
53. Vinogradova, Y., *et al.* Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. *BMJ.* **353** (2016).
54. Cai, T., *et al.* Associations between statins and adverse events in primary prevention of cardiovascular disease: Systematic review with pairwise, network, and dose-response meta-analyses. *BMJ* **374** (2021).
55. Erlandson, K. M. *et al.* Rosuvastatin worsens insulin resistance in HIV-infected adults on antiretroviral therapy. *Clin. Infect. Dis.* **61**, 1566–1572 (2015).
56. Lichtenstein, K. A. *et al.* Statin use is associated with incident diabetes mellitus among patients in the HIV outpatient study. *J. Acquir. Immune Defic. Syndr.* **69**, 306 (2015).
57. Spagnuolo, V. *et al.* Associations of statins and antiretroviral drugs with the onset of type 2 diabetes among HIV-1-infected patients. *BMC Infect. Dis.* **17**, 1 (2017).

Author contributions

N.N.V. conceived the original idea and refined it with K.O.B. and A.K. N.N.V. wrote the initial draft and K.O.B. conducted the data analysis. K.O.B. and A.K. contributed to subsequent drafts. All authors edited and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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