Lipid-lowering Efficacy of Statins in HIV-infected patients on Antiretroviral Therapy with Hypercholesterolemia: A meta-analysis of randomized controlled trials

Gladelyn C. Escasura, MD[1], Dastynne-Marie Dela Cruz, MD[2], Maria Adelaida M. Iboleon-Dy, MD, FPCP, FPCC, FACC, FAsCC[1,3]

[1]Dr. HB Calleja Heart and Vascular Institute, St. Luke's Medical Center, Quezon City, Philippines

[2]Department of Medicine, St. Luke's Medical Center, Quezon City, Philippines

[3]Heart Institute, St. Luke's Medical Center, Rizal Drive corner 32nd St., Bonifacio Global City, Taguig City, Metro Manila, Philippines

ABSTRACT

Introduction: There is no established treatment strategy among human immunodeficiency virus (HIV)-positive patients on antiretroviral therapy (ART) who developed hypercholesterolemia**.** We intended to assess the effect of statin use on hypercholesterolemia among HIV-infected patients on ART.

Methods: A meta-analysis was done on all randomized controlled trials (RCTs) that studied the effect of statins with placebo or antiretroviral switching on hypercholesterolemia of HIV-positive patients on ART. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used for the study selection process. Two authors independently abstracted the data. Mean difference (MD) were pooled using inverse-variance random-effect method. A number of sensitivity analyses were performed.

Results: Seven RCTs were included with a total of 272 HIV-infected patients receiving ART. Five of these studies have low risk of bias while two had high risk of bias. Statins significantly reduced fasting total cholesterol (TC) (WMD = -1.12, 95% CI = -1.27, -0.97, P<0.00001; WMD = -26.20, 95% CI = -41.63, -10.77, P=0.0009) and fasting low-density

lipoprotein-cholesterol (LDL-C) (WMD = -1.03, 95% CI = -1.66, -0.41, P=0.001; WMD = -23.34, 95% CI = -34.60, -12.08, P<0.0001) compared to placebo (after subgroup analysis) and ART switching.

Conclusion: Statins are effective in the treatment of hypercholesterolemia among HIV-infected patients on ART.

Keywords: statin, hypercholesterolemia, HIV, antiretroviral therapy

INTRODUCTION

Rationale

The introduction of antiretroviral therapy (ART) has radically increased the survival of Human Immunodeficiency Virus (HIV)-infected patients. However, the risk of coronary heart disease (CHD) is amplified as this population aged.[1] In addition, the incidence of sudden cardiac death is considerably higher in this population compared to the general population with comparable risk factors.[2] An elevated TG with a low HDL-C is the common lipid abnormality phenotype among this population mainly due to HIV infection per se.[3] Another possible explanation of this characteristic is the ART-induced increase in low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC) and triglycerides (TG).[4] Hence, HIV-patients have high predisposition for dyslipidemia and/or hypercholesterolemia which is a major modifiable risk factor that needs to be addressed properly.

However, the management of hypercholesterolemia/dyslipidemia in this population is a complex one. Various contributing factors must be considered including the HIV itself, the individual genetic characteristics, metabolic changes induced by

antiretroviral therapy, and drug-drug interactions.[5] In line with this, consensus guidelines provide varying recommendations regarding optimal strategy for treating hypercholesterolemia in HIV infection.[6,7]

Cardiology Guidelines like the European and American societies have mixed recommendations on the timing of starting statin therapy in this population. In the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, they recommend starting statin therapy in adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.7 to 4.8 mmol/L) who have a 10-year ASCVD risk of 7.5% or higher with Class of Recommendation (COR) of IIa and Level of Evidence (LOE) of B-Nonrandomized (B-NR).[3] In contrast, the 2016 ESC/EAC Guidelines recommends consideration of starting lipid-lowering therapy, mostly statins in HIV patients with dyslipidemia to achieve the LDL-C goal of <100mg/dL (2.6mmol/L) as defined for high risk subjects (COR: IIa; LOE: C).[8]

However, Infectious Disease societies in Europe and America have different recommendations. The revised 2013 HIV Medical Association (HIVMA) of the Infectious Disease Society of American (IDSA) Primary Care Guidelines and the AIDS Clinical Trials Group (ACTG) recommend using the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) for the management of Dyslipidemia in patients living with HIV. They recommend the use of statins to maintain LDL-C level <100mg/dL in for all groups except <70mg/dL for very high-risk patients.[9] The 2008 European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV provided a clear recommendation for the use of statin in this population. They recommend using statins to as first-line therapy to reduce raised

LDL-C levels to achieve target goals of different groups. For HIV-infected patients with Ischemic or Coronary Heart Disease (IHD or CHD) >20% in the next 10 years, prior Cardiovascular Disease (CVD), Type II Diabetes or Type I Diabetes with microalbuminuria, the target LDL-C cut-off level is ~115mg/dL (3mmol/L). For HIV-infected patients with IHD risk of 10-20% in the next 10 years, the target LDL-C cut-off level is ~155 mg/dL (4mmol/L). And lastly, for HIV-infected patients with IHD <10%, the target LDL-C cut-off level is ~190mg/dL (5mmol/L). Addition of fibrates is recommended only in cases of combined increased in LDL-cholesterol and triglyceride levels of >442 mg/dL (>5 mmol/L).[10]

Hence, a need exists for a meta-analysis that includes randomized controlled trials (RCTs) to provide concrete evidence to indicate the addition of statins in the standard antiretroviral regimen to provide greater improvement of hypercholesterolemia in HIV-infected patients.

Objectives

The primary objective of this study is to do a meta-analysis of randomized controlled trials to assess the efficacy of statins in the treatment of hypercholesterolemia in HIV-infected adults regardless of CHD risk.

METHODS

Overview

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for meta-analyses of healthcare interventions.

Eligibility criteria

Only studies that fulfilled the following criteria are included:

1) Types of studies: randomized controlled trials and crossover trials.
2) Types of participants: adults ≥ 18 years of age with documented HIV infection of either sex, with plasma HIV viral load of <50 copies/ml, with fasting TC level of >155mg/dL and/or LDL-C level of >80mg/dL[10], and on antiretroviral therapy.
3) Types of intervention: use of statins for treatment of hypercholesterolemia
4) Types of comparator: placebo or ART switching.
5) Types of outcome measures: mean/median change in fasting TC, and LDL-C.

The following are the exclusion criteria: pregnant, lactating women, history of allergic reaction with statins, elevated liver enzymes (aspartate transaminase or alanine transaminase >3 times the upper normal limit), and active liver disease.

Data sources and search strategy

The following databases were searched for eligible published and unpublished studies in English language on or before February 29, 2019: PubMed, Cochrane Library, EMBASE, BMJ Journals, Web of Science, ClinicalTrials.gov, HERDIN. The

following search terms were used: “statin”, “protease inhibitor switching”, “antiretroviral therapy”, “HIV”, and “hypercholesterolemia”.

Study selection

The study selection process followed the PRISMA guidelines. Abstracts only, duplicate studies, systematic reviews, non-English language, and studies that did not report changes in TC and/or LDL-C levels were excluded. Two authors (GCE and DMDC) independently reviewed the titles, abstracts, and full articles to determine whether studies met the inclusion criteria. Complete articles were obtained for all titles and abstracts that appear to meet the inclusion criteria. The reasons for exclusion was coded as one or more of the following: inappropriate population, inappropriate intervention, inappropriate comparison, inappropriate outcome(s), inappropriate study design, and other. Conflicting assessment between reviewers were resolved through discussion and review by a third author (MAID). A flow diagram that depicts the search process was shown in Figure 1.

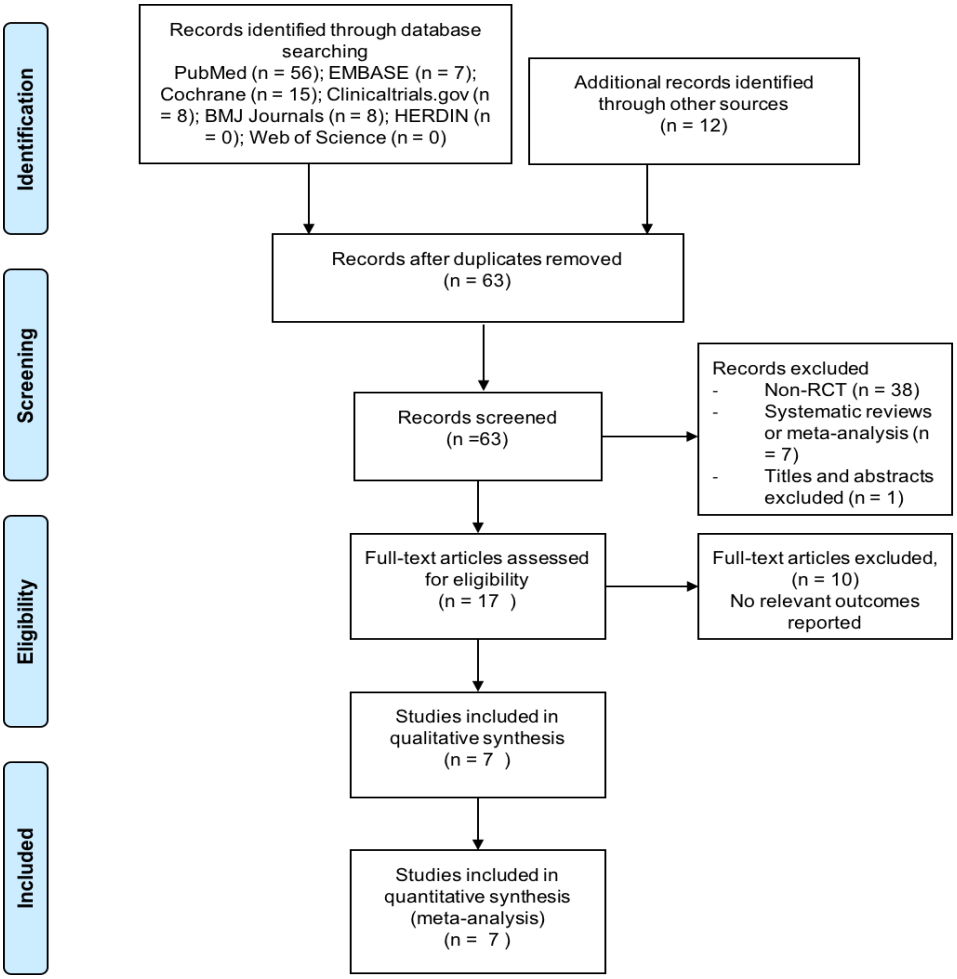


Figure 1. PRISMA Flow diagram of study selection process.

Data Extraction

The two authors (GCE and DMDC) independently abstracted data on study characteristics, participant characteristics, intervention characteristics, and outcome data for change in cholesterol levels (Table 1). The effect of statin therapy on LDL-C level as primary outcome and on TC level as secondary outcome were evaluated.

Quality Assessment

We graded the RCTs using the Quality Scale for Meta-Analytic Reviews (Table 2). The risk for bias for each RCTs were assessed using the Cochrane Risk of Bias

instrument. The bias in RCTs was evaluated for 6 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, and selective reporting. Sequence generation was considered as adequate if central randomization or tables of random numbers were used. Allocation concealment was considered as adequate if central randomization or sealed envelopes were used. We considered blinding as adequate if participants, outcome assessors, and statisticians were blinded from the group assignment. The other domains were assessed exactly as the criteria of the risk of bias tool. Each study was classified as having a high, low, or unclear risk of bias overall and for each domain. The overall risk of bias will be classified as high if any one of the domains is considered high risk.[11]

The two authors independently assessed the risk of bias of the included studies. Discrepancies were resolved by consensus. The third author was consulted if there was no consensus was reached. Table 2 showed the summary of risk of bias assessment. Sequence generation, allocation concealment, and blinding were considered as the key essential domains to score the overall quality of a trial.

Data synthesis and analysis

The meta-analysis was done using Review Manager version 5.3. Inverse-variance method was used for the analyses of continuous outcome data. The mean changes in TC and LDL-C were used to determine the efficacy of statin in treating hypercholesterolemia in HIV-infected patients. The continuous outcomes were pooled with mean difference and its corresponding 95% confidence intervals (CIs). The

statistical heterogeneity was assessed using I^2 test, wherein I^2 >50% was considered as significant heterogeneity. The random-effects model was applied to addressed the heterogeneity among studies.

Sensitivity analyses

The random-effects model and exclusion of a study were applied to addressed the heterogeneity among studies.

RESULTS

Search results

The literature search generated a total of 106 abstracts. Seven RCTs met the inclusion criteria. The detailed process of study selection is shown in Figure 1. Of the seven RCTs chosen, four RCTs compared statin with placebo, and three RCTs compared statin to ART switching. Included studies were either randomized parallel or crossover trials.

Study characteristics

A total of 272 HIV-infected patients treated in the seven RCTs published from 2004 to 2016 were included for this meta-analysis. Majority are males (82%), with a mean age of 46±9. All included patients have hypercholesterolemia with mean fasting TC of 287.8mg/dL±48.9 and mean fasting LDL-C of 173mg/dL±59. Hypertriglyceridemia was also noted with mean TG of 314.9mg/dL±200.1. The mean fasting HDL-C of

52.7mg/dL±23.0 was normal. The mean follow-up was 27 weeks±21. The baseline characteristics of the seven studies were presented in Table 1. Four RCTs compared statin as add-on drug (n = 57) to placebo (n = 57), while three RCTs compared statin (n = 62) to ART switching (n = 56). All included trials reported change in mean TC. However, one study (Mallon et al. 2006) did not report a baseline LDL-C hence changes in mean was not computed in this study.

Quality assessment of included studies

The quality of the studies and risk of bias assessment is shown in Table 2. High risk of selection bias was noted in two out of the seven studies. All four RCTs comparing statin to placebo graded A in terms of quality and rated to be at low overall risk of bias. All three RCTs comparing statin to ART switching received grade B in terms of quality. However, two out of the three RCTs was at high overall risk of bias due to its study design.

Table 1. Summary characteristics of included randomized controlled trials.

Study	Year	Country	Study Design	Mean Age, years	Male (%)	CHD Risk	Baseline Lipid Parameters (mg/dL), Mean (SD)	Follow-up duration	Control Group	Intervention Group	Outcome
Bonnet et al.[12]	2007	France	Double-blind, placebo-controlled RCT	43	85	Low	TC = 251.4 (23.2) LDL = 159.5 (14.7) TG = 236.9 (85.9) HDL = 36.7 (8.5)	12 weeks	Placebo (n=9)	Pravastatin (n=12)	Change in TG, TC, HDL, LDL
Lo et al.[13]	2015	USA	Double-blind, placebo-controlled RCT	51	80	High	TC = 195.5 (32.5) LDL 124.3 (34.4) TG = 116.9 (75.3) HDL = 51.2 (34.4)	48 weeks	Placebo (n=21)	Atorvastatin (n=19)	Change in TG, TC, HDL, LDL
Mallon et al.[14]	2006	Australia	Double-blind, placebo-controlled RCT	48	100	Moderate-high	TC = 293.9 (59.9) TG = 385.3 (527.0) HDL = 42.5 (15.5)	12 weeks	Placebo (n=17)	Pravastatin (n=16)	Change in TG, TC, HDL, LDL
Stein et al.[15]	2004	USA	Double-blind, placebo-controlled, crossover RCT	44	90	High	TC = 215.8 (15.5) LDL = 134.2 (12.4) TG = 334.8 (59.3) HDL 36.4 (2.7)	8 weeks	Placebo (n=10)	Pravastatin (n=10)	Change in TG, TC, HDL, LDL
Calza et al.[16]	2005	Italy	Open-label RCT	39	60	Low	TC = 266.8 (72.4) LDL = 100.5 (96.7) TG = 293.2 (106.1)	48 weeks	Nevirapine (NNRTI) (n=29)	Pravastatin (n=36)	Change in TG, TC, LDL
Lee et al.[17]	2015	Australia	Open-label, RCT	55	98	High	TC = 239.8 (46.4) LDL = 154.7 (34.8) TG = 194.9 (115.2) HDL = 46.4 (11.6)	12 weeks	Raltegravir (II) or Rilpivirine (NNRTI) (n=20)	Rosuvastatin (n=23)	Change in TC, LDL, HDL, TG

Wangpa-tharawanit et al.[18]	2016	Thailand	Unknown blinding, RCT	47	58	Moderate	TC = 551.8 (92.4) LDL = 302.8 (92) TG = 642.3 (431.6) HDL = 103.3 (34.4)	48 weeks	Atazanavir (PI) (n=25)	Atorvastatin (n=25)	Change in TC, LDL, TG, HDL

CHD = Coronary Heart Disease; NNRTI = Non-nucleoside reverse transcriptase inhibitor; II = Integrase inhibitor; PI = Protease inhibitor; TG = Triglyceride; TC = Total Cholesterol; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein

Table 2. Quality Scale Rating and Assessment of risk of bias of included randomized controlled trials.

Study	Quality Scale Rating (Grade)	Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel	Blinding of outcome assessment (detection	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Overall Risk of bias
Bonnet et al. 2007	A	+	+	+	+	+	+	+
Lo et al. 2015	A	+	+	+	+	+	+	+
Mallon et al. 2006	A	+	+	+	+	+	+	+
Stein et al. 2004	A	+	+	+	+	+	+	+
Calza et al. 2005	B	+	+	-	?	+	+	-
Lee et al. 2015	B	+	+	-	?	+	+	-
Wangpatharawanit et al. 2016	B	+	+	?	?	+	+	+

+ Low risk; - High risk; ? Unclear risk

Efficacy outcomes

All outcomes were analyzed using the inverse-variance random-effects model.

Comparison of changes in mean fasting total cholesterol, LDL, HDL and triglycerides between Statin and placebo

The pooled data of the four RCTs comparing statin to placebo showed that statin did not significantly reduce the mean fasting TC (WMD = -0.58, 95% CI = -1.36, 0.19, P

= 0.14; I^2 = 99%, P <0.00001). Same result was observed in the pooled data of the three RCTs that measure changes in LDL-C. No significant reduction in the mean fasting LDL with the use of statins (WMD = -0.55, 95% CI = -1.55, 0.45, P = 0.44; I^2 = 85%, P = 0.28) (Figure 2).

The substantial heterogeneity observed was possibly due to two studies with low to moderate-risk for CHD and reported no co-morbidities on enrolled patients. Pooled analysis with the exclusion of the two studies showed significant reduction of mean fasting TC (WMD = -1.12, 95% CI = -1.27, -0.97, P < 0.00001; I^2 = 0%, P = 0.41) and mean fasting LDL-C (WMD = -1.03, 95% CI = -1.66, -0.41, P = 0.001; I^2 = 0%, P = 0.37%) (Figure 3).

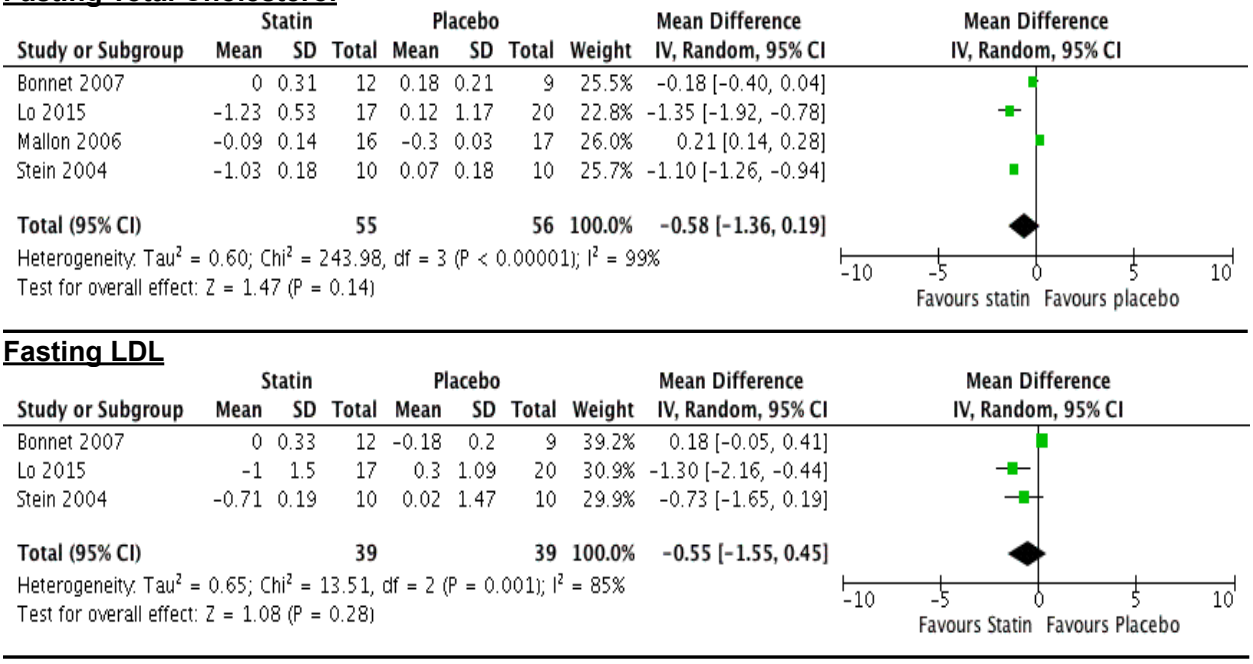
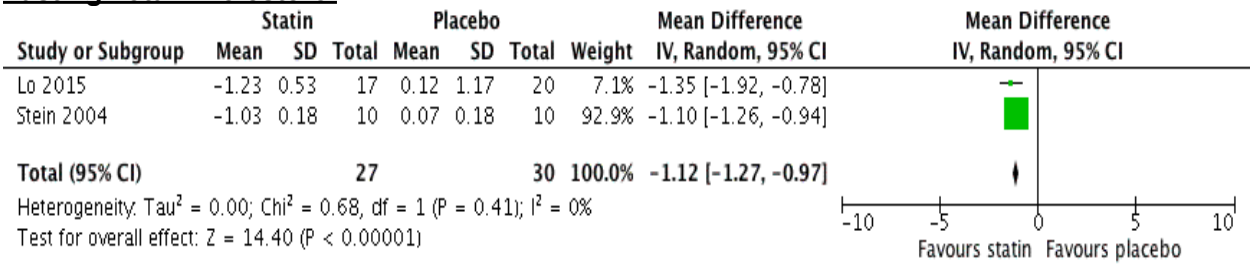


Figure 2. Effect of Statin versus placebo on mean fasting TC and LDL-C.

Fasting Total Cholesterol



Fasting LDL

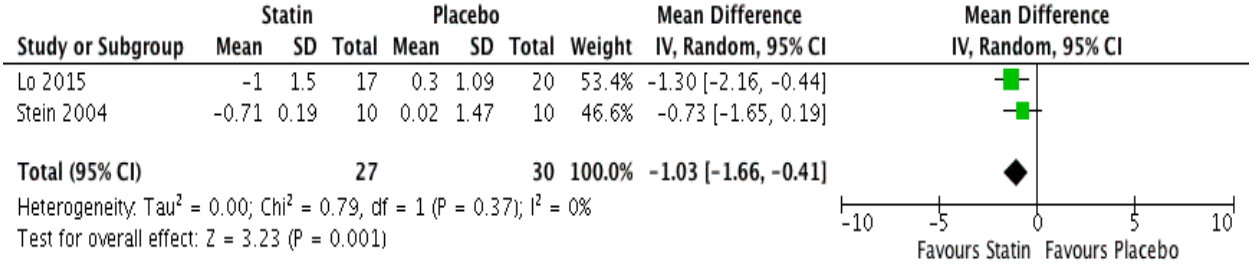


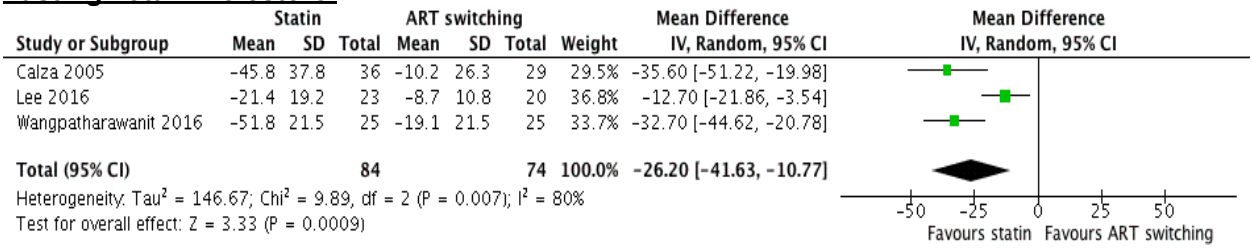
Figure 3. Subgroup analyses of the effect of statin versus placebo in changes of mean fasting TC and LDL-C.

Comparison of changes in mean fasting total cholesterol, LDL, HDL and triglycerides between Statin and ART switching

The pooled data of the three RCTs comparing statin to ART switching showed that statin significantly reduced the mean fasting TC by -26.20 (95% CI = -41.63, -10.77, P = 0.0009; I^2 = 80%, P <0.00001) (Figure 4). The substantial heterogeneity can be partly due to a smaller sample size of one of the included studies. Pooled analysis after removal of the study showed that statin still significantly reduced the fasting TC (WMD = -33.77, 95% CI -43.24, -24.29, P <0.00001; I^2 = 0%, P = 0.77) (Figure 5).

There is also significant reduction in fasting LDL-C with statin use (WMD = -23.34, 95% CI = -34.60, -12.08, P < 0.0001; I^2 = 68%, P = 0.04) (Figure 4). However, substantial heterogeneity was observed maybe due to one study with normal LDL-C level. After removal of the study, statin use still showed significant reduction in mean fasting LDL-C (WMD = -29.49, 95% CI = -38.61, -20.36, P <0.00001; I^2 = 0%, P = 0.92) (Figure 5).

Fasting Total Cholesterol



Fasting LDL

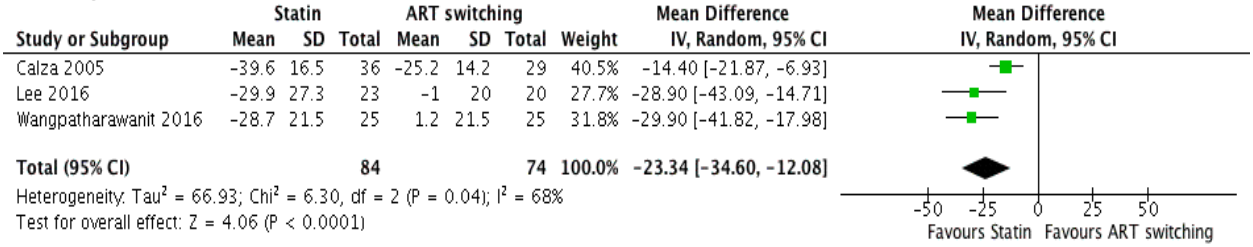
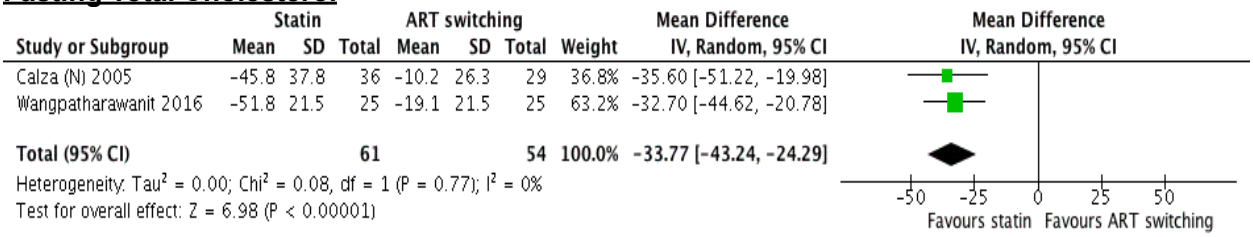


Figure 4. Effect of Statin versus ART switching on mean fasting TC and LDL-C.

Fasting Total Cholesterol



Fasting LDL

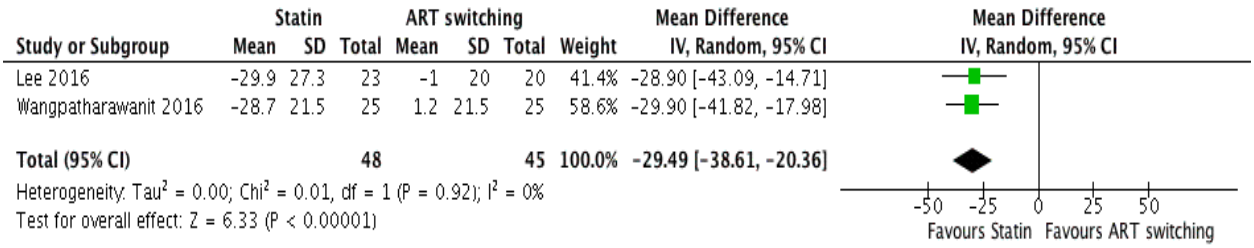


Figure 5. Subgroup analyses of the effect of statin versus ART switching in changes of mean fasting TC and LDL-C.

Risk of bias across studies

The substantial heterogeneity observed in all the analyses may be partly due to publication bias or within-study bias in smaller studies.

DISCUSSION

The main findings of our analysis is that statins significantly reduce the level of TC and LDL-C with or without ART switching in HIV-infected patients with hypercholesterolemia.

Dyslipidemia, defined as any abnormal serum lipid level, signifies a major cardiovascular (CV) risk for HIV-infected patients and consequently contributes to the rate of CV events in this population.[19] The current available antiretroviral drugs, especially PIs and NNRTIs, further contribute to the development of pro-atherogenic lipid profiles by altering lipid metabolism, aside from the disease per se. This explains the high prevalence of dyslipidemia and the complicated management of dyslipidemia in this population.[20]

Given the high predisposition of this population to develop this disease, we need to focus our intervention to modifiable factors in this complex disease. Hypercholesterolemia simply defined as presence of elevated plasma cholesterol levels with normal plasma triglycerides is one modifiable factor that could decrease the CHD risk among this population.[21] In the general population, the cut-off level for tagging hypercholesterolemia is a total blood cholesterol level of >200mg/mL and/or LDL-C level of ≥190mg/dL.[3,8]

Despite recommendations from AHA and ESC/EAS guidelines for the management of dyslipidemia in HIV patients, encouraging results of statins for primary prevention, switching of antiretroviral therapies and non-pharmacological interventions like diet and lifestyle modifications, there are still various recommendations with regards to strategy treatment of hypercholesterolemia in this population on ART.[18,19,20]

To our knowledge, our study is the first to provide a more definite evidence of the lipid-lowering efficacy of statins in the treatment of hypercholesterolemia with or without ART switching in HIV-infected patients on ART, with statins showing significant reduction in both TC and LDL-C levels. Our findings support that statins reduced the levels of LDL-C and TC. However, due to the substantial heterogeneity caused by presence of low quality studies and small number of patients, we cannot draw conclusions as to the effectiveness of statins in this population. Nevertheless, we can only hypothesize that the lipid-lowering effects of statins may lead to a better CV outcome in HIV-infected patients. The results of our meta-analysis contribute to the previously published meta-analyses of the use of statin in other high-risk groups.

Study limitations

There are several limitations in our meta-analysis that must be emphasized. First, the included RCTs in the meta-analysis have small sample size, thereby increasing the risk of bias. Second, the drug, dose, and the duration of the included trials were not homogenous which may lead to confounding bias. Third, the heterogeneity of the population included in the trials may have an impact on the reduction of TC and LDL making the results less generalizable. Lastly, three of the included studies have unclear risk of bias due to incomplete reporting of methods.

CONCLUSION

In HIV-positive patients on ART, statins were effective as treatment for hypercholesterolemia. Our findings are appropriate and reinforce the concept that statin lowers TC and LDL in this population as it is in other high-risk groups. However, more randomized controlled trials, especially those with bigger sample size, are needed to provide evidence of the benefit of statins as add-on drug for treatment of dyslipidemia and/or hypercholesterolemia in HIV-infected patients on ART.

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