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# Impact of antiretroviral therapy on serum lipoprotein levels and dyslipidemias: A systematic review and meta-analysis

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ABSTRACT

*Background:* Antiretroviral drugs increase biosynthesis and reduce hepatic clearance of serum cholesterol. It is thus important to evaluate the impact of antiretroviral treatment on serum lipoprotein levels and the risk of dyslipidemia.
*Methods:* We searched EMBASE and PubMed for articles comparing lipid profiles between HIV-infected adult patients naïve and exposed to antiretroviral therapy (ART). Eligible studies were pooled by performing random-effects meta-analyses of mean serum lipoprotein levels and prevalence estimates of dyslipidemias.
*Results:* 51 observational studies comprising 37,110 patients were included in the meta-analyses. ART-exposed patients had significantly higher concentrations of total cholesterol (45 studies, mean difference [MD] = 29.4 mg/dL, 95% confidence interval [CI] 26.5 to 32.4, $I^2 = 82.2\%$), low density lipoprotein-cholesterol (37 studies, MD = 14.9 mg/dL, 95% CI 11.2 to 18.5, $I^2 = 86.1\%$), and triglycerides (43 studies, MD = 46.8 mg/dL, 95% CI 37.8 to 55.8, $I^2 = 97.1\%$), compared with ART-naïve patients. The risks of hypercholesterolemia (25 studies, pooled odds ratio [OR] 3.8, 95% CI 3.1 to 4.7, $I^2 = 60.0\%$) and hypertriglyceridemia (21 studies, OR 2.2, 95% CI 1.7 to 2.9, $I^2 = 81.7\%$) were also significantly higher among ART-exposed patients, compared with ART-naïve patients.
*Conclusion:* Antiretroviral therapy is significantly associated with increase in serum lipid levels and increased risk of dyslipidemia. Whether or not these associations are causal should be investigated by future studies.


## 1. Introduction

Although deaths arising from AIDS-defining illnesses have declined substantially since the advent of highly active antiretroviral therapy (HAART) [1], increase in life-expectancy among people living with HIV may be associated with a rising incidence of cardiometabolic disorders—notably dyslipidemias—which are attributable to the adverse effects of some antiretroviral drugs [2–4]. While antiretroviral-naïve HIV-infected patients may have altered serum lipid levels as a result of the chronic inflammatory and platelet activating effects of HIV infection [5], studies suggest that antiretroviral treatment (ART) aggravates these effects by increasing biosynthesis and reducing hepatic clearance of serum lipids [3,6].

With an estimated 35 million people living with HIV worldwide, and over 2 million incident HIV infections annually [1], ART-associated dyslipidemias potentially constitute a global public health problem. In addition, prevalence estimates of dyslipidemia among ART-exposed HIV-infected persons have been reported to vary widely between 20% and 80% depending on the study design and population [7]. However, no systematic evidence has examined the effects of ART on lipid profile among people living with HIV. We, therefore, aimed to conduct a systematic review and meta-analysis of data regarding ART-associated changes in serum lipoprotein levels and dyslipidemia across various study-level characteristics. We also sought to examine factors that may potentially influence these associations.

## 2. Methods

### 2.1. Eligibility criteria

We included studies comparing serum lipoprotein levels and prevalence estimates of dyslipidemias between ART-exposed and ART-naïve HIV-infected adults (see Box 1 for inclusion and exclusion criteria). Two reviewers independently screened potentially eligible studies by their titles and abstracts. Where there were differences, agreement was reached by discussions with the other investigators.

### 2.2. Search strategy

We searched Embase and PubMed and Embase electronic databases from 1997 to 30 January 2015 for relevant articles. The search was conducted using medical subject heading (MeSH) terms and keywords: *HIV/, *highly active antiretroviral therapy/, *protease inhibitors/, HAART-naïve.mp., *dyslipidemias/, *hyperlipidemias/, *hypercholesterolemia/, *hypertriglyceridemia/, *total cholesterol/, *cholesterol blood level/, triglycerides.mp.,

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**Box 1**
Inclusion and exclusion criteria.

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Participants | HIV-infected adults | HIV-infected children and adolescents<br>HIV-negative |
| Exposure | ART-exposure versus ART-naïveté | ART-exposed and ART-naïve patients not reported |
| Outcomes | Serum lipoproteins (TC, TG, LDLc, HDLc) | Serum lipoproteins and dyslipidemias were not reported |
| | Hypercholesterolemia<br>Hypertriglyceridemia | |
| Study types | Cross-sectional studies | Expert reviews |
| | Cohort studies | Conference proceedings |
| | Randomized controlled trials | Policy reports |
| | Published data | Unpublished data |

ART—antiretroviral therapy; HDLc—high density lipoprotein cholesterol; LDLc—low density lipoprotein cholesterol; TC—total cholesterol; TG—triglycerides.

*triacylglycerol/, *high density lipoprotein cholesterol/. See eTables 1 and 2 for the full search strategies for Embase and PubMed respectively.

### 2.3. Data extraction

Two reviewers independently extracted data from each study using a piloted form and any discrepancies were also resolved by consensus with the other reviewers. Data extracted included article citation, country of origin, country income group, study design, sample size, mean age, proportion of females, proportion of current smokers and alcohol users, proportion of AIDS-defining illnesses, number of ART-exposed and ART-naïve patients, mean CD4 count, mean duration of ART, proportion of patients on protease inhibitors (PI), mean concentrations of lipoprotein parameters in ART-exposed and ART-naïve patients, and prevalence estimates of hypercholesterolemia and hypertriglyceridemia in ART-exposed and ART-naïve patients. Country income groups were defined according to World Bank development indicators [8]. Hypercholesterolemia was defined as serum total cholesterol levels of ≥240 mg/dL and hypertriglyceridemia as serum triglyceride levels of ≥150 mg/dL [9]. Where required, we estimated mean values (with standard deviations) from the median and range.

### 2.4. Assessment of risk of bias

The methodological quality of each study was assessed using a domain-based checklist adapted from the Cochrane risk of bias tool for non-randomized studies [10] [eTable 3]. Essentially, we categorized the risk of bias in each study as low, high or unclear according to five study areas: selection of participants (selection bias), assessment of exposure (information bias), outcome assessment (information bias), adjustment for confounding, and follow-up of participants in the cohort studies (attrition bias).

### 2.5. Statistical analysis

Due to anticipated differences in study methodology, we conducted meta-analyses using the DerSimonian–Laird random-effects model [11] to obtain overall and subgroup estimates: mean difference (MD) for serum lipoprotein levels and odds ratios (OR) for the dyslipidemias (hypercholesterolemia and hypertriglyceridemia). Heterogeneity across studies was assessed by inspecting forest plots using the $I^2$ statistic, for which a value of 50% indicated moderate heterogeneity [12]. We performed leave-one-study-out sensitivity analysis to determine the stability of the results. This analysis evaluated the influence of individual studies by estimating the weighted pooled estimate of the association by omitting a study at a time. We examined the associations between all study-level variables and the overall effect estimate for each outcome using meta-regression. Publication bias was assessed using Funnel's plot and Egger's tests for small-study effects [13]. Where publication bias was apparent, we ascertained its potential impact on the pooled estimates using the 'trim and fill' analysis of Duval and Tweedie [14]. Effect estimates were reported with 95% confidence intervals and exact p-values; we considered $p < 0.05$ as statistically significant. All analyses were conducted using Stata version 12 for Windows (Stata Corp, College Station, Texas).

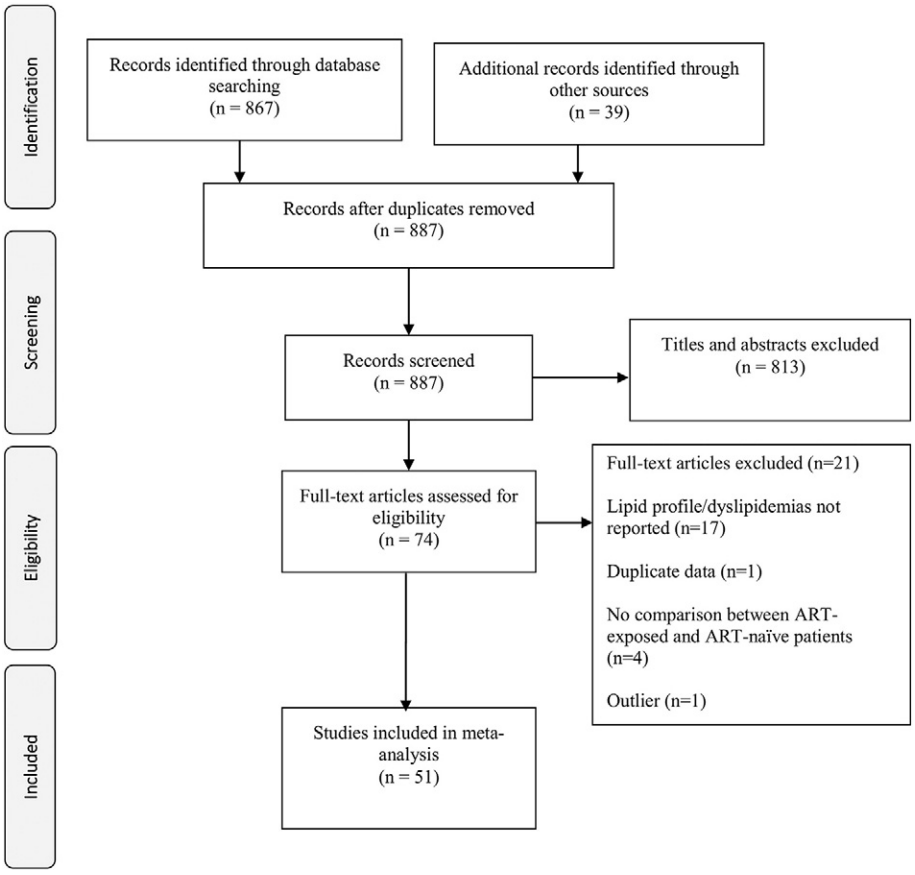


**Fig. 1.** Flow diagram showing study selection.