The management of dyslipidaemias in antiretroviral-treated HIV infection: a systematic review

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CRD summary
This review concluded that there is limited evidence to suggest that statins, fibrates, antiretroviral drug switching and perhaps metformin, may be useful for the management of dyslipidaemias in individuals infected with the human immunodeficiency virus who are undergoing highly active antiretroviral therapy. Overall, the authors' conclusions offer little insight into the available evidence and their reliability is questionable given the limited analysis and poor reporting of the review methods and data.

Authors' objectives
To determine the safety and efficacy of treatments for the management of dyslipidaemias, in human immunodeficiency virus (HIV)-infected individuals undergoing highly active antiretroviral therapy (HAART).

Searching
MEDLINE (via PubMed), EMBASE and the Cochrane CENTRAL Register were searched for English language articles published in the 5-year period up to 5 October 2005; the search terms were reported.

Study selection
Randomised controlled trials (RCTs) comparing interventions with the primary aim of improving the lipid profile of HIV-infected patients undergoing HAART were eligible for inclusion. Studies comparing different therapies, or comparing a therapy with placebo, were eligible. Paediatric studies and studies of antiretroviral-naive patients were excluded from the review, as were studies that did not report lipid levels as a primary outcome. The included studies evaluated the use of statins (pravastatin, fluvastatin and cholestin), fibrates (gemfibrozil, fenofibrate and bezafibrate), antiretroviral substitution (the majority of studies changed the protease inhibitor to abacavir or nevirapine) and insulin-sensitising drugs (metformin and rosiglitazone). Where reported, the participants were mainly adults aged at least 18 years old, with viral loads ranging from <50 to <10,000 cells/µL and CD4 cell counts ranging from >100 to >350 cells/µL. Baseline antiretroviral therapies varied between the studies; further details were reported in the review.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study validity was assessed using the methodology checklists of the Scottish Intercollegiate Guidelines Network. Trial duration, predetermined calculations of statistical power, allocation concealment, number of drop-outs, baseline similarity of treatment groups and use of an intention-to-treat analysis were reported in the review.

The authors did not state how the validity assessment was performed.

Data extraction
Only statistically significant effect sizes for efficacy outcomes were extracted; comparisons were made between different treatment arms or between baseline and follow-up. The percentage change from baseline in the most clinically relevant lipid levels were extracted: i.e. triglycerides (Trig), total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, high-density lipoprotein (HDL) cholesterol and non-HDL cholesterol, and the ratio of total cholesterol to HDL cholesterol. If these were not reported, attempts were made to calculate values from the reported study data. Adverse event data were also extracted.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
Methods of synthesis
No real synthesis of the evidence was carried out. Data tables presented the overall direction, and in some cases the significance of the effect, for each treatment arm in the individual studies. Some differences between the studies were evident from the data tables.

Results of the review
Thirteen RCTs (n=733), two of which were placebo-controlled, were included in the review.

Where reported, 2 trials were double-blinded and seven were open-labelled. Four trials used an intention-to-treat analysis and a further two were assumed to have done so. All but 2 trials failed to carried out an assessment of statistical power, and one of the two aforementioned trials failed to recruit sufficient numbers of patients to achieve 80% power. Where reported, losses to follow-up were minimal (usually one or two participants per treatment arm), with the exception of 2 trials of antiretroviral substitution where overall withdrawals were 24% and 23%; 2 trials reported no drop-outs.

Statins (3 RCTs).
One RCT reported collective reductions from baseline in Trig (34.8%), TC (25.2%) and LDL cholesterol (25.9%), with an increase in HDL cholesterol (23.9%), for pravastatin and fluvastatin, but no statistically significant differences between the two treatment arms. Similarly, a second RCT reported no statistically significant differences in TC between pravastatin with dietary advice and dietary advice alone. A third RCT reported decreases in TC (12%) and LDL cholesterol (23%) for cholestin, compared with increases in TC (4.1%) and LDL cholesterol (25.1%) for the placebo control.

Fibrates (3 RCTs).
One RCT reported collective reductions from baseline in Trig (40.7%), TC (21.9%) and LDL cholesterol (22.5%), with an increase in HDL cholesterol (19.9%), for gemfibrozil, fenofibrate and bezafibrate, but no statistically significant differences between the treatment arms. A second RCT reported reductions from baseline in Trig (40%), TC (14%), non-HDL cholesterol (17%) and LDL cholesterol (14%), with an increase in HDL cholesterol (15%), for fenofibrate, but no significant changes from baseline for vitamin E. A third RCT reported no statistically significant differences in lipid levels between gemfibrozil and placebo.

Antiretroviral substitution (6 RCTs).
All 6 RCTs reported that switching antiretrovirals was associated with overall reductions from baseline in a number of different lipid parameters, along with accompanying increases in HDL cholesterol. Positive effects were greater when switching from a protease inhibitor to abacavir versus continuing with a protease inhibitor (2 RCTs), and when switching from a protease inhibitor to efavirenz (1 RCT) or nevirapine (3 RCTs) versus continuing with a protease inhibitor.

Insulin sensitisers (1 RCT).
One RCT of metformin and rosiglitazone reported a 22% decrease in fasting Trig from baseline to follow-up in the metformin arm, whilst increases in TC (23%), LDL cholesterol (28%) and HDL cholesterol (38%) from baseline to follow-up were reported for the rosiglitazone arm.

Adverse events (13 RCTs).
Four trials (2 statin trials, an antiretroviral substitution trial and the insulin sensitiser trial) reported no adverse events. A further 4 trials (one statin, one fibrate and two antiretroviral substitution) reported no appreciable or significant differences in adverse events between the treatment and control arms. The remaining trials reported a variety of adverse events but many were mild or experienced by small numbers of participants; further details were reported in the review.
Authors' conclusions
There is limited evidence relating to the management of dyslipidaemias in HIV-infected patients undergoing HAART. However, the available trials suggest that statins, fibrates, antiretroviral drug switching and, perhaps, metformin are suitable for this indication, but larger trials are required before any recommendations can be made.

CRD commentary
This review answered a clear review question, but may have missed relevant data by only including studies published in English; this potentially leads to both language and publication bias. The authors also limited their searches to a 5-year period, but made no attempt to justify or explain this restriction. The review methods were poorly described and it is unclear whether appropriate precautions were taken to reduce the risk of reviewer error and bias when selecting studies, assessing study validity and extracting the study data. Study characteristics and data were summarised in tables, and attempts were made to assess the quality of the studies, although the reporting of this assessment was limited. Some differences between the studies are evident from the data tables, but there was no real attempt to synthesise or discuss the study data beyond what is presented in these tables. There was also no consideration of the results within the context of study validity or heterogeneity. The data extracted and presented in the summary tables appears to focus on the direction, and on occasions the significance, of lipid level changes from baseline to follow-up. Data comparing lipid level changes between the different treatment arms is missing in some cases, as is the statistical significance of any differences, which limits the analysis. Overall, the authors' conclusions offer little insight into the evidence and their reliability is questionable given the limited analysis and poor reporting of the review methods and data.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further larger clinical trials are required before any recommendations about management strategies can be made. In particular, trials are needed to investigate the optimal durations of therapies, including whether therapies should be lifelong, and to investigate the efficacy and safety of other treatments such as diet and/or exercise, niacin, fish oil, ezetimibe and human recombinant growth hormone. The authors also highlighted a number of methodological weaknesses which should be considered when designing future trials: small sample sizes, no predetermined calculation of statistical power, and baseline differences between study groups.

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