Effects of first-line use of nucleoside analogues, efavirenz, and ritonavir-boosted protease inhibitors on lipid levels

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CRD summary
This review found that there was a wide range of lipid elevations during 48 weeks of ritonavir-boosted protease inhibitors or efavirenz in antiretroviral-naive patients, depending on the type of antiretrovirals used. The reliability of the conclusions is unclear due to a lack of reporting of the review process, lack of validity assessment, and unclear suitability of the data synthesis methods.

Authors' objectives
To evaluate the effects of the first-line use of efavirenz, nucleoside analogues, and ritonavir-boosted protease inhibitors on lipid levels in antiretroviral-naive patients.

Searching
The electronic database MEDLINE was searched (dates were not reported), and drug labels and conference abstracts were also examined; search terms were reported. The US Food and Drug Administration product labels were also searched for registration trials of each approved antiretroviral and for abstracts of clinical trials presented at five conferences.

Study selection
Clinical trials were eligible for inclusion if they studied at least 50 antiretroviral-naive patients for at least 48 weeks and used a ritonavir-boosted protease inhibitor (where the daily dose of ritonavir was 100 to 200mg) or efavirenz combined with a fixed pair of nucleoside analogues. Data had to be available on the mean or median levels of total cholesterol, triglycerides, low-density lipoprotein (LDL), and high density lipoprotein (HDL) at baseline and at week 48.

The included studies compared ritonavir-boosted protease inhibitors with each other or ritonavir-boosted protease inhibitors with non-boosted protease inhibitors or evaluated lopinavir boosted with ritonavir (with and without nucleoside reverse transcriptase inhibitor backbones) or fosamprenavir boosted with ritonavir. The protease inhibitors used, doses and frequency of medication varied between studies. The mean age of the included participants ranged from 34 to 40 years, where described, and the majority of the participants were male. The percentage of Caucasian patients ranged from 36 to 78. The use of lipid-lowering drugs was reported in four trials.

The authors did not state how the papers were selected for the review, nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The change in each lipid parameter from baseline to 48 weeks was calculated for each trial and treatment arm, along with the associated 95% confidence interval. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The mean lipid changes were combined and weighted by inverse-variance, to produce estimates of 48-week elevations in each lipid parameter. The trials were combined in two groups according to the use of different nucleotide reverse transcriptase inhibitor backbones (tenofovir with emtricitabine versus abacavir, stavudine, or zidovudine each used with lamivudine). For each lipid parameter meta-regression analyses were conducted, in which the relative effects of protease inhibitors or efavirenz versus the nucleoside analogues were assessed. Backwards stepwise regression was used to reduce the variables in the models, while retaining the treatment group.
The models were used to estimate the mean lipid levels within each combination of protease inhibitor, efavirenz, and nucleotide reverse transcriptase inhibitor group. The regression analyses did not report any differences in lipid elevation between saquinavir, darunavir, or atazanavir when boosted with ritonavir, so these protease inhibitors were grouped (group one ritonavir-boosted protease inhibitors). There were also no significant differences in lipid elevation between fosamprenavir and lopinavir when boosted with ritonavir so these were also grouped (group two ritonavir-boosted protease inhibitors).

**Results of the review**

Fifteen trials, with 26 trial arms, were included (6,367 patients).

**Total cholesterol**: There was no significant difference in total cholesterol rises between groups one and two ritonavir-boosted protease inhibitors, or between group one ritonavir-boosted protease inhibitors and efavirenz. The use of stavudine, zidovudine or abacavir as nucleoside reverse transcriptase inhibitors was associated with higher increases in total cholesterol than the use of tenofovir (p<0.0001).

**Triglycerides**: The mean rise from group one ritonavir-boosted protease inhibitors was 39mg per dL (95% CI 33 to 44) lower than from trials of ritonavir-boosted lopinavir and ritonavir-boosted fosamprenavir (p<0.0001) and was 10mg per dL (95% CI 3 to 16) higher than from trials with efavirenz (p=0.005). The mean increase in triglycerides was 23mg per dL higher (95% CI 19 to 27) for patients who received abacavir, stavudine or zidovudine with lamivudine, compared with those who received tenofovir with emtricitabine.

**HDL and LDL**: There were no differences between ritonavir-boosted protease inhibitors and efavirenz in LDL levels. There was a larger rise in LDL level for patients who received abacavir, stavudine or zidovudine with lamivudine (10mg per dL, 95% CI 4 to 17) compared with those who received tenofovir with emtricitabine. For HDL, antiretroviral treatment had no effect on absolute changes from baseline. The percentage change in HDL (from baseline) was significantly less with efavirenz than with ritonavir-boosted protease inhibitors (-10%, 95% CI -20 to -1) and more with tenofovir with emtricitabine compared with abacavir, stavudine or zidovudine with lamivudine (11%, 95% CI 4 to 15).

**Authors' conclusions**

There was a wide range of lipid elevations during 48 weeks of first-line highly active antiretroviral therapy, which depended on the type of antiretrovirals used.

**CRD commentary**

The review question was supported by inclusion criteria for participants, intervention, outcomes, and study design. Published and unpublished sources were searched, reducing the possibility of publication bias. It was not reported whether language restrictions were applied, so the possibility of language bias could not be assessed. The authors did not describe whether the review processes were performed in duplicate nor how disagreements were resolved, so it is not known whether reviewer error and bias were possible. The quality of the primary studies was not assessed so their reliability, and the reliability of their results, is not known. Heterogeneity between studies was not assessed, so it is unclear whether pooling was appropriate.

Due to a lack of reporting of the review process, lack of validity assessment, and unclear suitability of the data synthesis methods, the reliability of the authors' conclusions is unclear.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that more research was needed to show whether lipid elevations, or other markers, significantly altered the cardiovascular risk for the different antiretrovirals.

**Funding**
Bibliographic details

PubMedID
19362991

DOI
10.1310/hct1001-1

Original Paper URL
http://thomasland.metapress.com/content/284897866402462/?p=085d17f0055048aeb05bde912079217a& amp;pi=0

Indexing Status
Subject indexing assigned by NLM

MeSH
Antiretroviral Therapy, Highly Active; Benzoxazines /therapeutic use; Cholesterol /blood; Cholesterol, HDL /blood; Cholesterol, LDL /blood; Clinical Trials as Topic; HIV Infections /drug therapy; HIV Protease Inhibitors /blood /therapeutic use; Humans; Nucleosides /therapeutic use; Reverse Transcriptase Inhibitors /therapeutic use; Ritonavir /therapeutic use; Triglycerides /blood

AccessionNumber
12009105167

Date bibliographic record published
09/09/2009

Date abstract record published
21/04/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.