Initial highly-active antiretroviral therapy with a protease inhibitor versus a non-nucleoside reverse transcriptase inhibitor: discrepancies between direct and indirect meta-analyses

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CRD summary
This review evaluated the effectiveness of initial highly-active antiretroviral therapy (HAART) with a protease inhibitor (PI) and a non-nucleoside reverse transcriptase inhibitor (non-NRTI). The authors concluded that non-NRTI-based HAART is more effective than PI-based HAART for virological suppression, but the interventions are similar for clinical outcomes. Despite some possible limitations, the conclusions are likely to be reliable.

Authors' objectives
To evaluate the effectiveness of initial highly-active antiretroviral therapy (HAART) with a protease inhibitor (PI) and a non-nucleoside reverse transcriptase inhibitor (non-NRTI) in a direct comparison meta-analysis.

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched from 1997 to October 2005; the search terms were reported. In addition, references were screened and relevant journals (the Journal of Acquired Immunodeficiency Syndrome, Clinical Infectious Diseases and the Journal of Infectious Diseases) and conference proceedings were handsearched. No language restrictions were applied. Abstracts were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that lasted at least 24 weeks were eligible for inclusion in the review.

Specific interventions included in the review
Studies that evaluated one of the following comparisons: two NRTIs plus one non-NRTI versus two NRTIs plus one PI; two NRTIs plus one non-NRTI versus two NRTIs; or two NRTIs plus one PI versus two NRTIs. The included studies administered combinations of lamivudine, abacavir, efavirenz, amprenavir, zidovudine, didanosine, stavudine, nelfinavir, zalcitabine, nevirapine, indinavir, delavirdine, atazanavir and saquinavir; the PI was given with or without ritonavir.

Participants included in the review
Studies of human immunodeficiency virus-infected antiretroviral-naive patients (with no previous antiretroviral treatment), or patients with limited antiretroviral exposure (up to 14 days exposure to non-NRTIs or PIs, less than 6 months’ exposure to zidovudine, didanosine, zalcitabine or stavudine, or previous exposure to NRTIs in less than 80% of patients), who were at least 16 years old were eligible for inclusion. The majority of the included studies were conducted in antiretroviral-naive patients. Where reported, the patients had a mean age of 33 to 43 years, 7 to 35% were female, and 5 to 76% were non-white.

Outcomes assessed in the review
The studies had to report one or more of the following outcome rates (based on intention-to-treat data): death, new acquired immunodeficiency syndrome (AIDS)-defining events, virological suppression and withdrawals because of adverse events. Clinical progression was defined as the proportion of patients with a new Center for Disease Control and Prevention stage C event; virological success was defined as the proportion of patients with a viral load of less than 50 copies/mL. The mean or median CD4 count increase (cells/mm2) was also reported.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
Two reviewers independently assessed the adequacy of the randomisation method, allocation concealment, blinding and the reporting of withdrawals. Any discrepancies were resolved by consensus.

Data extraction
The reviewers extracted patient population characteristics (e.g. baseline viral load and proportion of participants with AIDS), study design features (e.g. handling of switching of antiretroviral drugs), drug regimen and outcomes at the latest follow-up. Where the defined outcomes were not reported, the reviewers consulted study authors, funding sources, or publicly available Food and Drug Administration documents. If the information was not available, the reviewers abstracted information about drug discontinuations due to adverse events, or serious adverse events (grade 3 or 4, or as defined by investigators) instead of withdrawals and used either less sensitive measures (more than 50 copies/mL) or other study defined outcomes for virological failure (such as relapse). The outcomes were reported as odds ratios (ORs). In addition, interventions were categorised according to the initial regimen when studies reported pre-planned sequences of HAART or allowed antiretroviral switches. The results from groups assessing the same type of regimen were combined when trials compared three or more relevant antiretroviral regimens.

Methods of synthesis
How were the studies combined?
A random-effects model was used to calculate pooled ORs for the direct, head-to-head, comparisons of studies in the presence of statistical significant heterogeneity. Adjusted indirect pooled ORs (adjusted by the results of their comparisons against the common intervention of two NRTIs; the variance was estimated as the cumulative variance of the natural log of the OR) were calculated for indirect comparisons. The difference between direct and indirect estimates was estimated by calculating the difference in log ORs (p<0.05 was considered significant). The risk of publication bias was evaluated by assessing funnel plot asymmetry using the Egger test and the trim-and-fill method.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test (with p<0.10) and the I-squared statistic. Subgroup analyses of more specifically defined antiretroviral regimens were carried out in the presence of heterogeneity. Sensitivity analyses based on univariate meta-regression analysis explored several study level covariates and quality aspects; significant variables (p<0.05) were entered into a multivariate regression model and backwards eliminations were carried out to derive the final model. In addition, a cumulative random-effects meta-analysis was used to assess the stability of the estimates.

Results of the review
Twenty-six trials (n=7,379) were included in the review: 12 trials compared two NRTIs plus one non-NRTI versus two NRTIs plus one PI (n=3,337); 8 trials compared two NRTIs plus one PI versus two NRTIs (n=2,897); 6 trials compared two NRTIs plus one non-NRTI versus two NRTIs (n=1,145).

Quality.
Nineteen of the 26 studies did not describe the randomisation method used; the remaining studies used computer-generated methods. Sixteen of the 26 studies did not report the method of allocation concealment; the remaining studies were rated as adequate. Half of the studies were described as open-label studies; the remaining studies were described as blinded. Seventeen of the 26 studies reported withdrawals and drop-outs; the rest only partially reported or failed completely to report withdrawals and drop-outs.

There was evidence of funnel-plot asymmetry for the outcome virological suppression.

Direct comparisons.
Non-NRTI-based regimens were superior to PI-based regimens regarding virological suppression (OR 1.60, 95% CI: 1.31, 1.96, p<0.00001; based on 12 studies). There was evidence of statistical heterogeneity (I-squared 39%).
difference was reduced in higher quality trials. Non-NRTI-based regimens were not statistically significantly superior to PI-based regimens in terms of the number of deaths or disease progressions. There were also no differences in withdrawals because of adverse events.

Indirect comparisons.

The indirect analysis found NNRTI-based HAART to be worse than PI-based HAART for the outcome virological suppression (OR 0.26, 95% CI: 0.07, 0.91; 26 studies). The discrepancy between the indirect and direct estimates was statistically significant (p=0.005).

Authors’ conclusions

Direct analyses suggested that non-NRTI-based HAART is more effective than PI-based HAART for virological suppression and is similar to PI-based HAART for clinical outcomes. Indirect comparisons could be unreliable for rapidly evolving and complex interventions such as HAART.

CRD commentary

The review addressed a clear research question and stated clear inclusion criteria. The searches encompassed the identification of published and unpublished trials without language restrictions, thereby reducing the risk of publication and language bias. However, the authors’ own assessment of publication bias suggested that such a bias may exist for virological suppression. Furthermore, the reviewers followed up relevant outcome data not reported in the primary publications. The quality of the included studies was assessed and used in sensitivity analyses. The review reported measures to reduce bias and errors in the quality assessment but not in other stages of the review.

The included studies were described in detail, allowing a clear overview of the existing evidence. The analyses were thorough, comparing direct and indirect comparisons and investigating the effects of a variety of variables on the results. Some pooled outcomes showed statistical significant heterogeneity; the authors explored heterogeneity in further analyses. The conclusions are likely to be reliable, but some limitations to the interpretation of results may remain (e.g. publication bias cannot be ruled out; some of the pooled results showed evidence for statistical heterogeneity).

Implications of the review for practice and research

Practice: The authors stated that providers should be cautious about making treatment decisions based on indirect analyses because of the potential for clinically significant discrepancies between indirect and direct treatment comparisons; indirect comparisons should always be verified as sufficient direct evidence becomes available.

Research: The authors stated that robust head-to-head trials which are reported according to CONSORT (Consolidated Standards of Reporting Trials) guidelines are required.

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