Nevirapine or efavirenz combined with two nucleoside reverse transcriptase inhibitors compared to HAART: a meta-analysis of randomized clinical trials
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Authors' objectives
To estimate the overall effectiveness and tolerability of antiviral therapy in human immunodeficiency virus (HIV)-infected patients, and the additional benefit related to the inclusion of non-nucleoside reverse transcriptase inhibitors (non-NRTIs) in the treatment.

Searching
The authors searched MEDLINE, Internet sources, and international conference presentations, mainly the Interscience Conference on Antimicrobial Agents and Chemotherapy, the Conference on Retroviruses and Opportunistic Infections, and the AIDS International Conference, from January 1994 to June 2000.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Antiviral therapies for HIV-infected patients using two NRTIs and one or two protease inhibitors (PIs) were included. This association was formerly called 'highly active antiviral therapy' (HAART), but the definition of HAART has subsequently been extended to include the association of two NRTIs and one non-NRTI. The review was later divided to allow the separate assessment of comparisons of three-drug regimens based on two NRTIs and one non-NRTI (nevirapine or efavirenz) with (1) two-drug regimens based on two NRTIs and (2) three-drug regimens based on two NRTIs and one PI (HAART).

Participants included in the review
Adults receiving antiviral therapy for HIV infection were included.

Outcomes assessed in the review
Three outcomes were assessed from the available data, although the authors do not differentiate which, if any, was the primary outcome. The outcomes were: the rate of patients with undetectable viral load at the end of the follow-up period (16 to 48 weeks from the start of the treatment); the rate of patients with clinical progression of HIV disease, determined as death or occurrence of opportunistic events during the follow-up period; and the reported rate of adverse events (graded as 2 or more). The viral load assays had cut-offs ranging from 20 to 500 copies/mL. When viral load was assessed by assays of different sensitivities, the most sensitive method was considered.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following data were tabulated: previous antiretroviral treatment; baseline CD4+ count; log baseline viral load (assay...
cut-off); treatment; the number of patients; and the duration of follow-up for each study. The data were extracted into one of two overall groups: trials comparing three-drug regimens (two NRTIs and one non-NRTI) with two-drug regimens (two NRTIs); and trials comparing both three-drug regimens (two NRTIs and one non-NRTI versus two NRTIs and one PI).

To obtain an overall measure of the efficacy of antiretroviral regimens, the odds ratios (ORs) were estimated for every outcome and for each trial. Intention to treat analysis was used for efficacy outcomes, in which patients who discontinued treatment were considered to have no response.

**Methods of synthesis**

*How were the studies combined?*

The ORs calculated for each outcome and for each trial were combined to provide an estimate of the overall OR, according to the method described by Yusuf et al. (see Other Publications of Relevant Interest). Ninety-five per cent confidence intervals (CIs) were determined for the OR, and the Mantel-Haenszel two-tailed chi-squared test was used to evaluate statistical significance. The authors do not state whether publication bias was assessed.

*How were differences between studies investigated?*

The chi-squared test for heterogeneity was performed to assess whether the effect of variation of treatment across the RCTs was greater than that expected by chance. Patient characteristics in each study were also compared qualitatively. In addition, separate analyses were performed for naive versus experienced patients, and for asymptomatic versus advanced HIV infection, where these were found to differ.

**Results of the review**

Eleven RCTs were included in the review. Six RCTs compared three-drug regimens based on two NRTIs and one non-NRTI with two-drug regimens based on two NRTIs. Five RCTs compared three-drug regimens based on two NRTIs and one non-NRTI with three-drug regimens based on HAART (two NRTIs and one PI).

For the RCTs comparing three- and two-drug regimens, 2,130 participants were eligible. After excluding those treated with monotherapy, or with one NRTI plus one non-NRTI, 1,722 participants were included in the analysis. For the RCTs comparing both three-drug regimens, 1,027 patients were enrolled. After excluding those treated with a non-NRTI plus PI, or with three NRTIs, 730 participants were included in the analysis.

RCTs comparing three-drug regimens (two NRTIs and one non-NRTI) with two-drug regimens (two NRTIs).

Of the patients treated with the non-NRTI regimen, 58.2% had a virological response compared with 22.2% of those treated with two NRTIs (OR 3.6, 95% CI: 2.2, 6.0, p <0.0001; heterogeneity, p=0.14). Virological response was observed in 34.9% of the nevirapine-treated patients (OR 3.6, 95% CI: 1.7, 7.3, p=0.004; heterogeneity, p=0.29) and in 76.3% of the efavirenz-treated patients (OR 3.6, 95% CI: 1.8, 7.4, p=0.0003; heterogeneity, p=0.037). Undetectable viraemia was observed in 69.4% of the naive patients (OR 5.2, 95% CI: 2.8, 9.7, p=0.0001; heterogeneity, p=0.22).

A fair reduction of HIV disease progression was also observed in nevirapine-treated patients (OR 0.8, 95% CI: 0.6, 1.0, p=0.06; heterogeneity, p=0.15). A significantly lower rate of HIV progression of 40.6% was observed in patients with advanced HIV infection (CD4+ lymphocyte count below 100/mm3) who were treated with non-NRTIs, compared with 48.7% of those treated with two NRTIs (OR 0.7, 95% CI: 0.5, 0.9, p=0.024; heterogeneity, p=0.79).

RCTs comparing both three-drug regimens: two NRTIs and one non-NRTI versus HAART (two NRTIs and one PI).

Virological response was observed in 61.8% of the patients treated with two NRTIs and one non-NRTI, compared with 50.7% of those treated with HAART (OR 1.6, 95% CI: 1.1, 2.1, p=0.0028; heterogeneity, p=0.0198). No significant differences were found between the two interventions for the rate of disease progression (OR 0.7, 95% CI: 0.2, 2.0, p=0.81; heterogeneity, p=1.0).

Adverse events were observed in 47.5% of the patients treated with two NRTIs and one non-NRTI, and in 53.7% of those treated with HAART (OR 0.6, 95% CI: 0.4, 0.9, p=0.03; heterogeneity, p=0.009). A rash was observed in 10.9%.
of those treated with two NRTIs and one non-NRTI, and in 3.9% of those treated with HAART (OR 2.8, 95% CI: 1.4, 5.4, p=0.002; heterogeneity, p=0.51).

Authors' conclusions
Triple therapy with two NRTIs and one non-NRTI seemed to be more effective than therapy with two NRTIs at reducing viral load. Furthermore, treatment with two NRTIs and one non-NRTI yielded a slightly better virological response and was better tolerated than HAART. Additional data are needed to support the use of triple therapy with non-NRTIs as first-line therapy in experienced patients and patients with advanced HIV.

CRD commentary
The review question was clear. With the exception of study design, which specified that studies had to be RCTs, the study selection criteria were not stated clearly. The search of electronic databases was limited to MEDLINE, while an additional reference to 'Internet sources' was not clarified further. Some effort was made to find unpublished sources or relevant conference presentations. The authors provided no description of the methods used to select the literature, assess validity, or extract the data. The outcomes evaluated were stated clearly and the statistical methods described seem appropriate and adequate. The results of the heterogeneity test were reported in full, but there were no details of whether publication bias was addressed. There are results reported in the abstract which appear different from those appearing in the main results section (e.g. the reported ORs for virological response rate for naive patients).

The authors' conclusions appear appropriate in the light of the data presented in the paper.

Implications of the review for practice and research
Practice: The authors state that non-NRTIs (mostly nevirapine and efavirenz) are promising drugs for the treatment of HIV infection because they have good antiretroviral activity, are generally well tolerated, and can be administered once a day, although data supporting their use in clinical practice are still limited. However, there is no definitive direct evidence that the natural history of the disease, including delayed progression to AIDS or death is significantly modified by non-NRTI treatment.

Research: The authors state that further research is needed to provide additional data to support the use of triple therapy with non-NRTIs as first-line therapy in experienced patients and those with advanced HIV disease.

Bibliographic details
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Other publications of related interest

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