Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults

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Authors' objectives
To estimate the effectiveness of triple combination therapy in antiretroviral-naive adults.

Searching
MEDLINE was searched from 1994 to 2000 using the following keywords: 'clinical trial', 'plasma HIV-1 RNA', 'highly active antiretroviral therapy', 'antiretroviral therapy' and 'naive'. In addition, all clinical trials presented in the package insert for approved antiretroviral drugs were included. The following conferences were also reviewed for relevant trials: Interscience Conference on Antimicrobial Agents and Chemotherapy; Conference on Retroviruses and Opportunistic Infections; International AIDS Conference; European Conference on Clinical Aspects and Treatment of HIV Infection; and the Annual Meeting of the Infectious Disease Society of America.

Study selection
Study designs of evaluations included in the review
Clinical trials were included in the review. All studies must have been at least 24 weeks in duration. In addition, they had to have either reported the percentage of patients with undetectable HIV RNA using the Roche Amplicor or Chiron bDNA assays in an intention to treat analysis, or provided sufficient data to enable the calculation of intention to treat results. Other studies were excluded for the following reasons: AG-511, plasma HIV-1 RNA was unavailable for the study population; and BI-1090, ACTG193A, and ACTG261, plasma HIV-1 RNA data were unavailable for the subset of naive patients.

Specific interventions included in the review
Triple combination therapy was defined as a dual nucleoside reverse transcriptase inhibitor (NRTI) and either (1) a protease inhibitor (PI triple); (2) a non-nucleoside reverse transcriptase inhibitor (NNRTI triple); or (3) a third NRTI (triple NUC). Further details relating to the regimens were provided in the paper.

Participants included in the review
Human immunodeficiency virus (HIV). Only studies that included at least 30 chronically HIV-infected adult patients who were antiretroviral-naive or had very limited prior antiretroviral exposure (at most 2 weeks prior NRTI exposure) were included.

Outcomes assessed in the review
The primary outcomes of interest appear to have been changes in plasma HIV RNA level and CD4 cell count, and the variability of treatment response across different drug classes.

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
No formal assessment of quality was undertaken.

Data extraction
Two independent reviewers extracted the following information on the characteristics of the trial design and the study population, and on the response rates.
Trial design characteristics: treatment regimen; open-label or blinded design; whether or not randomisation was used; whether or not the trial contained a concurrent control group; and average daily pill burden, defined as the nominal number of tablets or capsules per day (including placebo) in the prescribed treatment regimen.

Baseline and disease characteristics of the study population: the number of patients enrolled; the percentage of men; racial and ethnic distribution; median age; median log10 baseline plasma HIV RNA level; and median baseline absolute CD4 cell count.

Response rate: the percentages of patients with a plasma HIV RNA level of less than or equal to 50 and less than or equal to 400 copies/mL at 24 and 48 weeks, where available; and the actual change from baseline in CD4 cell count at 24 and 48 weeks. The former (percentage of patients) were recalculated if necessary using the intention to treat method. The latter (absolute change in CD4 cell count) was abstracted using the last observation carried forward or on an as-treated basis. If median values were unavailable then the mean was used. The results of the two reviewers were compared and differences were reconciled. The intention to treat methods used were presented in the paper.

Methods of synthesis
How were the studies combined?
A fixed-effect model was used to synthesise the data, whereby each result was weighted in direct proportion to the number of patients contributing data to the analysis. The 95% confidence intervals (CIs) were constructed for the mean response rate using the derived weighted mean and its variance.

How were differences between studies investigated?
The 95% CIs for the pairwise differences between drug classes were constructed for the mean response rate using the derived weighted mean and its variance. The statistical significance of the differences in mean response rates across drug classes was assessed using an asymptotic test based on the normal distribution. The variability in treatment group response rates was assessed using a simple weighted linear correlation analysis and by weighted least-squares regression using a backwards stepwise selection procedure. Variability was assessed as a function of the following: population baseline CD4 cell count, population median baseline log10 plasma HIV RNA, antiretroviral triple drug class, and average daily pill burden. Logarithmic transformation of the predictor and response variables was used to stabilise the variance of the response variables.

Results of the review
Twenty-three trials were included in the review, of which 19 were randomised controlled trials. Twelve trials were open-label and 11 were double-blind. The total numbers of patients included in the review were not reported.

Over all trials, the median log10 baseline plasma HIV RNA averaged 4.69 (49,329 copies/mL) and the CD4 cell count averaged 375E6 cells/L.

The overall estimated percentage of patients with plasma HIV RNA less than or equal to 400 copies/mL at 24 weeks was 64% (95% CI: 60, 67). The percentage of patients with plasma HIV RNA less than or equal to 50 copies/mL at 48 weeks was 46% (95% CI: 41, 52) for PI triple, 51% (95% CI: 43, 59) for NNRTI triple, and 45% (95% CI: 36, 54) for triple NUC.

The CD4 cell count increase over all trials at 24 and 48 weeks averaged +123E6 cells/L (95% CI: 111E6, 135E6) and +160E6 cells/L (95% CI: 146E6, 175E6), respectively, and did not differ between drug classes.

In multivariate regression analysis, neither the baseline plasma HIV RNA level and CD4 cell count nor treatment regimen predicted a plasma HIV RNA level of less than or equal to 50 copies/mL at week 48. However, pill count was significantly negatively associated with a plasma HIV RNA level of less than or equal to 50 copies/mL at week 48 (p=0.0085).

Authors' conclusions
The results suggested that the three drug regimens containing two NRTI with a PI, a NNRTI, or a third NRTI may
provide comparable activity. Practical issues, such as daily pill burden, should be considered when choosing a treatment regimen.

**CRD commentary**

The review question was clearly stated and the inclusion criteria were sufficient to allow replication of the review. The search was also adequate although only one database was searched, presenting the possibility that not all studies have been identified. In addition, there were no attempts to identify unpublished material and publication bias was not formally assessed. No formal quality assessment was performed, although design characteristics were extracted and the data extraction was checked until a consensus was reached. There was no information relating to the number of reviewers involved in selecting the papers, thus it is not known whether any bias had been introduced at this stage. Only limited details of the included studies were reported; it is therefore difficult for the reader to verify the authors' findings.

In many ways this was a well-conducted review and the authors' conclusions appear to follow from the summaries presented. However, the lack of detail concerning the primary studies raises concerns over the reliability of the conclusions.

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

The authors did not state any implications for further research and practice.

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