Systematic review and meta-analysis of evidence for increasing numbers of drugs in antiretroviral combination therapy

Jordan R, Gold L, Cummins C, Hyde C

Authors' objectives
To assess the effectiveness of increasing the numbers of drugs in antiretroviral combination therapy.

Searching
MEDLINE, the Cochrane Library, EMBASE, CINAHL, PsycLIT, and HealthSTAR were searched up to the end of February 2001. Appropriate Internet sites such as AIDSTRIALS were searched, as were citation lists. Pharmaceutical companies were also contacted. Studies reported in any language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) lasting at least 12 weeks were eligible.

Specific interventions included in the review
Comparisons of any licensed (United Kingdom or United States) antiretroviral therapy drug (or combination) with any other antiretroviral drug, placebo or no treatment were eligible. Interventions lasting less than 12 weeks were excluded. The actual comparisons were of triple versus double therapy, double versus monotherapy, and monotherapy versus placebo or no treatment. The most common double therapies were two nucleosides, with the most common comparison therapy being zidovudine or didanosine monotherapy. The triple therapies were most commonly two nucleosides (usually zidovudine plus didanosine or lamivudine) with a protease inhibitor or a non-nucleoside. The duration of the trials ranged from 12 weeks to 4.8 years. Unusual therapies such as cyclical or intermittent therapies were excluded.

Participants included in the review
Human immunodeficiency virus (HIV). The participants were patients who were positive for any stage of HIV, were aged at least 12 years, and with less than 6 months' previous antiretroviral therapy. Studies in which less than 30% of patients had undergone therapy previously, and studies that reported the results separately for patients who had never had therapy, were also included. Over 80% of the participants were male, and the average age ranged from 27 to 40 years. Most of the patients were asymptomatic, with baseline CD4 counts ranging from 83 to 660 cells/microL and mean viral load ranging from 2.35 to 7.35 log copies/mL.

Outcomes assessed in the review
The primary outcomes were clinical outcomes (changes in disease progression or death) and surrogate outcomes (CD4 count and plasma viral load).

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
Validity was assessed using the criteria described by the NHS Centre for Reviews and Dissemination (see Other Publications of Related Interest no.1). The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Two independent reviewers extracted the data. Tables providing details such as the trial name and treatments compared...
are available on the BMJ website (accessed 21/10/2002). See Web Address at the end of this abstract. Viral loads and CD4 counts were measured at the longest time point, when at least half of the total number of patients in each arm remained. The treatment effect for continuous outcomes was calculated for individual trials as the difference in mean change (treatment minus control). In trials with several treatment arms, the number of events and the number of participants were weighted so that each participant was used only once.

**Methods of synthesis**

**How were the studies combined?**

Studies were grouped according to the regimens compared. The continuous data were pooled using the inverse variance method of weighting. The event rates were pooled using the fixed-effect method of Yusuf et al. (see Other Publications of Related Interest no.2), to give pooled odds ratios (ORs) and 95% confidence intervals (CIs). Significance was set at a p-value of less than 0.05 for event rates. Publication bias was assessed visually using a funnel plot, and statistically using Egger's and Begg's tests.

**How were differences between studies investigated?**

Statistical heterogeneity was assessed using the chi-squared test. Heterogeneity was investigated using sensitivity and subgroup analyses and fixed-effect weighted regression techniques, using the following factors as covariates: trial duration; baseline CD4 count or viral load; drop-out rates; drug dose; specific drug or drugs (protease inhibitors or zidovudine); change in CD4 count or viral load; sensitivity of the viral load assay; and blinding and concealment of allocation.

**Results of the review**

Fifty-four RCTs (20,404 patients) were included.

The trials were generally of a good quality. In one third of the trials, concealment of allocation was confirmed; most were double-blind; and the treatment groups were comparable within trials. Follow-up was not always clearly reported (additional data presented on the BMJ website; see Web Address at end of abstract).

**Quadruple therapy:** no fully published evidence on the effectiveness of quadruple or higher therapies was found.

**Monotherapy (zidovudine) versus placebo or no treatment** (18 comparisons, 7,929 patients). Zidovudine significantly reduced disease progression or death (OR 0.7, 95% CI: 0.6, 0.8). Significant heterogeneity was found (chi-squared 25.47, d.f.=14, Z=5.02). Heterogeneity was partly explained by the duration of the trials; as trials increased in length, zidovudine had a smaller relative effect. Zidovudine resulted in an improved CD4 count of 47 cells/microL (95% CI: 29, 65) and no significant heterogeneity was found. The viral load was also significantly reduced with zidovudine but significant heterogeneity was found.

**Double therapy versus monotherapy** (16 comparisons, 5,084 patients).

Double therapy significantly reduced disease progression or death when compared with monotherapy (OR 0.6, 95% CI: 0.5, 0.7). Significant heterogeneity was found (chi-squared 22.16, d.f.=15, Z=6.44). Heterogeneity appeared to be largely accounted for by one large RCT of protease inhibitors, but excluding this RCT did not alter the results. The duration of the trials did not explain the heterogeneity. Double therapy led to significantly improved results for CD4 counts and viral load when compared with monotherapy. Significant heterogeneity was found for both outcomes, but this was wholly accounted for by the presence of zidovudine or protease inhibitors. Triple therapy versus double therapy (9 comparisons, 3,671 patients).

Triple therapy significantly reduced disease progression or death when compared with double therapy (OR 0.6, 95% CI: 0.5, 0.8). Most trials had few events. Significant heterogeneity was found (chi-squared 8.52, d.f.=8, Z=4.21).

Heterogeneity appeared to be largely accounted for by one open-label RCT, but excluding this RCT did not alter the results. Triple therapy led to significantly improved results for CD4 counts and viral load when compared with double therapy. Significant heterogeneity was found for both outcomes. The possible causes were quality criteria, i.e. concealment of allocation and non-blinding, and the types of drugs used.
There was no consistent visual or statistical evidence of publication bias, except for CD4 count for triple versus double therapy.

Drop-outs (26 RCTs).

The drop-out rates were higher with monotherapy compared with placebo, but were similar between double and monotherapy. The results for triple therapy compared with double therapy were inconsistent. The quality of life results (4 RCTs) were inconsistent.

Authors' conclusions
The evidence from RCTs supports the use of triple therapy. Research is needed on the effectiveness of quadruple therapies and the relative effectiveness of specific combinations of drugs.

CRD commentary
This was a clearly written and presented review. The aims were clearly stated and the inclusion criteria were defined in terms of the study design, participants, intervention, and outcomes. Several relevant sources of trials were searched, no language restrictions were applied, and the possibility of publication bias was assessed. However, the keywords used were not stated, and the methods used to select the studies were not described.

The eligible studies were restricted to RCTs and their quality was formally assessed using validated criteria. The methods used to extract the data were described whereas those used to assess validity were not. The studies were grouped according to comparison therapies and the data were pooled in a meta-analysis. However, the finding of significant statistical heterogeneity suggested that the meta-analysis was not an appropriate means of combining some of the data. Potential causes of this heterogeneity were explored, and sensitivity analyses examined the influence of various factors (including validity criteria) on the results. Few studies assessed quality of life. The assessment of adverse reactions was limited to comparisons of drug-related drop-out rates between treatment regimens.

The evidence presented supports the authors' conclusions, but the presence of significant heterogeneity suggests that the results should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors state that the review supports the use of triple therapy but that there is inadequate evidence for quadruple or higher combinations.

Research: The authors state that research is required on the effectiveness of quadruple therapies and the relative effectiveness of specific combinations of drugs. They also state that future studies should be designed more rigorously and should be less variable, e.g. in trial duration, test drugs, comparators, and clinical stage of trial entry. In addition, future studies should not evaluate only surrogate outcomes.

Funding
UK West Midlands NHS Regional Public Health Levy.

Bibliographic details

PubMedID
11923157

Original Paper URL
Other publications of related interest

This additional published commentary may also be of interest. Rutherford GW. Increasing the number of drugs in antiretroviral therapy may improve survival in people with HIV infection. Evidence-based Healthcare 2002;6:163-4.

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-HIV Agents /administration & dosage; Clinical Trials as Topic /standards; Drug Administration Schedule; Drug Therapy, Combination; HIV Infections /drug therapy; Humans; Publication Bias; Randomized Controlled Trials as Topic /standards; Treatment Outcome

AccessionNumber
12002008205

Date bibliographic record published
31/10/2002

Date abstract record published
31/10/2002

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.