

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

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Abstract

Objective To assess the evidence for the effectiveness of increasing numbers of drugs in antiretroviral combination therapy.

Design Systematic review, meta-analysis, and meta-regression of fully reported randomised controlled trials. All studies included compared quadruple versus triple therapy, triple versus double therapy, double versus monotherapy, or monotherapy versus placebo or no treatment.

Participants Patients with any stage of HIV infection who had not received antiretroviral therapy.

Main outcome measures Changes in disease progression or death (clinical outcomes); CD4 count and plasma viral load (surrogate markers).

Search strategy Six electronic databases, including Medline, Embase, and the Cochrane Library, searched up to February 2001.

Results 54 randomised controlled trials, most of good quality, with 66 comparison groups were included in the analysis. For both the clinical outcomes and surrogate markers, combinations with up to and including three (triple therapy) were progressively and significantly more effective. The odds ratio for disease progression or death for triple therapy compared with double therapy was 0.6 (95% confidence interval 0.5 to 0.8). Heterogeneity in effect sizes was present in many outcomes but was largely related to the drugs used and trial quality.

Conclusions Evidence from randomised controlled trials supports the use of triple therapy. Research is needed on the effectiveness of quadruple therapies and the relative effectiveness of specific combinations of drugs.

Introduction

In 1987 zidovudine was introduced for the treatment of HIV infection. Since then there has been an escalation in the number of antiretroviral agents. Sequentially, treatment with two and then three drugs has become rapidly accepted.¹⁻⁵ Treatment with four or more drugs has also been proposed.^{3, 6}

Systematic reviews have examined questions about the effectiveness of specific drugs and combinations or have included trials with a mixture of patients who

have and have not received drug treatment.⁷⁻¹² We carried out a systematic review on the effectiveness of increasing numbers of drugs used in combination. To reduce the potential for confounding by established drug resistance we looked only at those patients who had not previously received antiretroviral therapy.

Methods

Search strategy and inclusion criteria

We looked for randomised controlled trials of antiretroviral therapy in HIV patients (up to the end of February 2001) in Medline, the Cochrane Library, Embase, CINAHL, PsycLIT, Healthstar, appropriate internet sites such as AIDSTRIALS, and citation lists. We also contacted pharmaceutical companies. We included studies only if they included patients who were HIV positive (any stage) and were aged ≥ 12 years with less than six months' previous antiretroviral therapy or if less than 30% of patients had previous therapy or if patients who had never had therapy were reported separately. The accepted interventions were any licensed (United Kingdom or United States) antiretroviral drug (or combination) compared with any other antiretroviral drug or placebo or no treatment. We excluded studies if they lasted less than 12 weeks. We assessed studies for quality using a standard checklist.¹³

Analysis

Data were collected on all relevant outcomes, with disease progression and deaths as clinical outcomes and CD4 count and viral load as surrogate markers. To take account of the large dropout rates but to maximise the length of time in the trial we measured CD4 count and viral load at the longest time point when at least half the total number of patients in each arm remained. For continuous outcomes (CD4 count and viral load change) we calculated the treatment effect for individual trials as the treatment effect (that is, mean change) minus the control effect. We pooled data using the inverse variance method of weighting (for continuous outcomes) and the fixed effects Peto method for event rates.¹⁴ Significance was set at $P < 0.05$. We assessed statistical heterogeneity using the χ^2 test.^{15, 16} When there were several arms within a trial we

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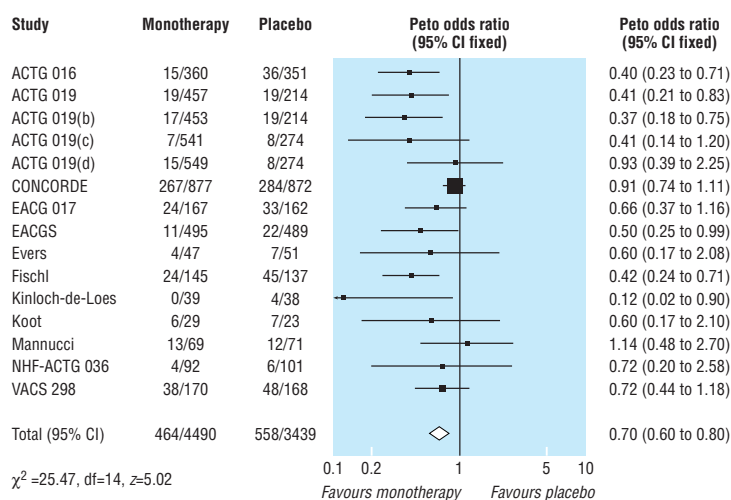


Fig 1 Effect of zidovudine monotherapy versus placebo on disease progression or death. Figures are number of events/number of participants

weighted the number of events and the number of participants so that each participant was used only once.

We explored heterogeneity using sensitivity and subgroup analyses and fixed effects weighted regression techniques, with the covariates of trial duration, baseline CD4 count/viral load, dropout rates, drug dose, specific drug or drugs (presence of protease inhibitors or zidovudine), change in CD4/viral load, sensitivity of the viral load assay, and blinding and concealment of allocation.

We assessed publication bias visually using a funnel plot and statistically using Egger's and Begg's tests.

Results

Quantity, quality, and characteristics of trials

Out of over 2000 search "hits" we retrieved 700 papers and finally included 90, which referred to 54 different trials and 20 404 patients (references for these 54 trials can be found in the long version of this paper on bmj.com; selected references are cited here). Over 80% of the participants were men, with an average age ranging between 27 and 40 years. More patients were asymptomatic than at any other clinical stage, mean baseline CD4 counts ranged from 83-660 cells per μ l, and mean viral load ranged from 2.35 to 7.35 log copies per ml. The length of the trials varied from 12 weeks to 4.8 years, although follow up was not always clearly reported.

Zidovudine was the only monotherapy compared with placebo or no treatment. The most common dual therapies were two nucleosides, most which were compared against zidovudine or didanosine monotherapy. Triple therapies were mainly based on the currently advised pattern of two nucleosides (usually zidovudine plus didanosine or lamivudine) with the addition of a protease inhibitor or a non-nucleoside. One trial compared quadruple therapy with protease inhibitors at lower doses to boost each other rather than as true quadruple combination and therefore was not incorporated into the analyses.¹⁷

Potential publication bias

We found no consistent visual or statistical evidence of publication bias except for CD4 count for triple versus double therapy, where there was a clear lack of small studies with negative results.

Main outcomes

Monotherapy compared with placebo

Compared with placebo, zidovudine significantly reduced disease progression or death (odds ratio 0.7, 95% confidence interval 0.6 to 0.8), although there was substantial heterogeneity (fig 1). Zidovudine also resulted in an improvement in CD4 count of 47 cells per μ l (29 to 65) with no important heterogeneity and a viral load reduction of 0.56 log copies per ml (0.71 to 0.41) with some unexplained heterogeneity. The heterogeneity present in the clinical outcome data (range of odds ratio 0.1-1.1, fig 1) was in part explained by the variable duration of the trials: as the trials increased in length zidovudine had a smaller relative effect. At 152 weeks (about three years), as in the Concorde trial,¹⁸ the beneficial effect of zidovudine was virtually eliminated (fig 2).

Double therapy compared with monotherapy

Double therapy resulted in significantly better clinical outcomes than monotherapy did (odds ratio for disease progression/death was 0.6, 0.5 to 0.7, fig 3). There was some heterogeneity, but this seemed to be largely accounted for by one large trial of protease inhibitors.¹⁹ Sensitivity analysis in which we excluded this trial did not alter the effect size or confidence intervals. The trial duration did not explain the heterogeneity.

Results for surrogate markers were significantly better with double therapy than with monotherapy. Heterogeneity in the CD4 counts was wholly accounted for by the presence of zidovudine or protease inhibitors, which suggests that combinations that contain protease inhibitors may be more effective than other double therapies and that monotherapy with zidovudine is less effective compared with other monotherapies. Heterogeneity was present in the analysis of viral load, but exploratory analyses were not informative.

Triple therapy compared with double therapy

Triple therapy significantly improved clinical outcomes compared with double therapy (odds ratio for disease

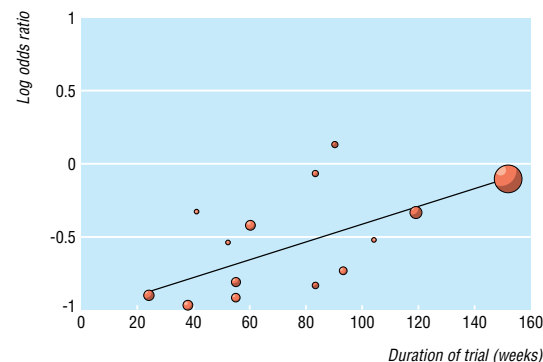


Fig 2 Duration of trial and odds of disease progression or death with zidovudine monotherapy versus placebo

progression/death was 0.6, 0.5 to 0.8, fig 4), although most trials had few events. Only one large trial lasted over a year, and this contributed most events.²⁰ The heterogeneity was attributable to one open label study with few events.²¹ In a sensitivity analysis that excluded this study we found no change in the estimates of effect size. The results for the surrogate markers (CD4 and viral load) were consistent with those for the clinical outcomes, showing that triple therapy was significantly better than double therapy, though there was substantial heterogeneity in all analyses. Possible causes of this heterogeneity were issues of quality (concealment of allocation and non-blinding) and types of drugs used.

Other outcomes

Twenty six trials gave information on drug related withdrawals. Dropout rates were higher with monotherapy than with placebo but no different between double therapy and monotherapy. The results of triple compared with double therapy were heterogeneous. There was no significant difference in dropout rates between triple therapy without a protease inhibitor and double therapy without a protease inhibitor. Trials of therapies that contained a protease inhibitor in the triple but not the double arm had significantly higher withdrawals, with one exception.²⁰ Only four trials gave useful information regarding quality of life related to health,^{22–26} and they had inconsistent results.

Discussion

This systematic review of combination therapy for people with HIV showed a consistently and significantly greater benefit for increasing numbers of drugs up to, and including, triple therapy for clinical outcomes and surrogate markers. There was, however, marked heterogeneity, mainly accounted for by the drugs tested and issues of quality.

Strengths and weaknesses

HIV patients who have never received antiretroviral drugs comprise only a part of clinical practice, but establishment of the effectiveness of such treatment in these patients is fundamental to understanding the overall relative benefit of the drugs, and subsequent treatment decisions are contingent on the initial choice. Though choice of this study population reduced confounding, other potential causes of clinical heterogeneity were reflected in the results. Exploration of heterogeneity with regression techniques suggested that different drugs might explain some of the variation. This conclusion must be tempered with caution as post hoc analyses are purely exploratory and the techniques used are limited, with small numbers of observations. Data on individual patients would allow better exploration of the effect of patient characteristics, although such techniques are usually too expensive and time consuming.²⁷ In addition, some of these findings are based on surrogate end points and should be confirmed by clinical end points, which are less well reported in published trials. Data on adverse events are difficult to interpret in the context of HIV trials in which patient behaviour may differ from clinical practice, and a full evaluation of adverse events should include postmarketing surveillance. Despite a rigorous search for trials, the possibility of publication bias cannot be completely excluded.

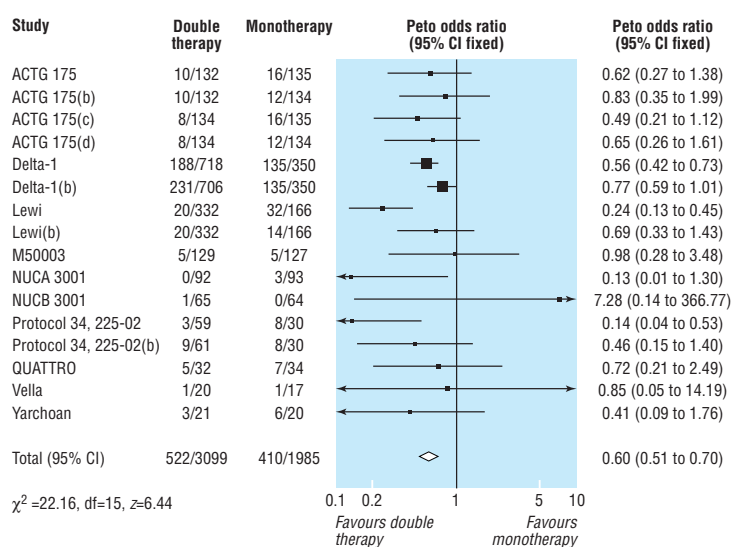


Fig 3 Effect of double therapy versus monotherapy on disease progression or death. Figures are number of events/number of participants

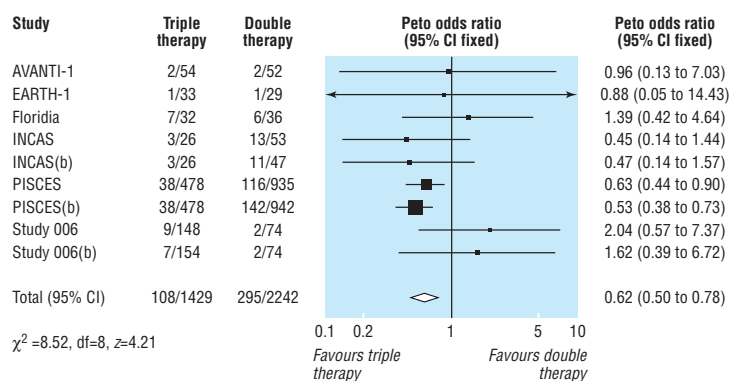


Fig 4 Effect of triple therapy versus double therapy on disease progression or death. Figures are number of events/number of participants

Implications and future research

This systematic review provides new evidence that the escalation of combinations of antiretroviral drugs up to triple therapy is an effective strategy. Our results for the relative effectiveness of monotherapy versus placebo and double therapy versus monotherapy are consistent with the results of smaller meta-analyses.^{11 12} Also, the overall findings are supported by the results of cohort studies.^{28–33} However, there is no fully published evidence on the effectiveness of quadruple or higher combinations.

Future work to clarify which triple combination is the most effective is as important as investigating the effectiveness of quadruple or higher combinations. As the number of drugs increases, quality of life and safety assume relatively greater importance but are currently inadequately reported.

The exploratory analyses of heterogeneity indicate that the design of future trials must be more rigorous and less variable (for example, in trial duration, test drugs, comparators, and clinical stage at entry) and should not rely on surrogate outcomes alone. There are still important questions to be answered about the

What is already known on this topic

Triple combination antiretroviral therapy is accepted by clinicians and patients as the usual treatment for HIV and has evolved through an incremental strategy in the numbers of drugs combined

Guidance on treatment, however, has predominantly been based on early reports of research

There are no published analyses that assess the effectiveness of the increasing numbers of drugs used in combination

What this study adds

The results of this systematic review support the use of triple therapy but there is inadequate evidence for quadruple or higher combinations

Heterogeneity in the effect estimates seems to result from variable effectiveness of different drug combinations, trial duration, and problems with study quality

effectiveness of existing agents. This may require publicly funded trials which should be carried out within a clear well supported collaborative framework.

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Endpiece Ugly editor needed

"Annette McDwyer is doing research for a documentary about people who are described as ugly. She would like to speak to Richard."

Note found on his desk by Richard Smith, editor of the *BMJ*