

Clinical efficacy of antiretroviral combination therapy based on protease inhibitors or non-nucleoside analogue reverse transcriptase inhibitors: indirect comparison of controlled trials

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Abstract

Objective To compare the clinical efficacy of triple antiretroviral regimens based on protease inhibitors and non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) in adults positive for antibodies to HIV-1.

Design Systematic review and meta-analysis using indirect comparisons of clinical trials comparing three drug regimens based on two nucleoside reverse transcriptase inhibitors (NRTIs) and either a protease inhibitor or an NNRTI with two drug regimens (two NRTIs). Participants had no previous exposure to protease inhibitors or NNRTIs.

Data sources Medline, the Cochrane controlled trials register, Aidstrial, Aidsdrugs, conference proceedings, and trial registers.

Main outcome measure Progression to AIDS or death.

Results 14 trials, totalling 6785 patients, were identified. Most patients had been exposed to an NRTI and had advanced immunodeficiency at baseline; 1096 progressed to AIDS or died. Seven trials assessed protease inhibitors based triple regimens and seven assessed NNRTI based triple regimens (nevirapine or delavirdine). Triple therapy was more effective than dual therapy. The effect was pronounced for protease inhibitor based regimens (odds ratio 0.49, 95% confidence interval 0.41 to 0.58) but non-significant for NNRTI based regimens (0.90, 0.71 to 1.15). Indirect comparison of the two regimens gave an odds ratio of 0.54 (0.49 to 0.73) in favour of protease inhibitor based treatments. Increases in CD4 cell counts were smaller and suppression of viral replication less with NNRTI based regimens.

Conclusions Indirect evidence shows that protease inhibitor based triple regimens are superior to regimens based on the NNRTIs nevirapine and delavirdine in patients with advanced immunodeficiency who have been exposed to NRTIs. Large trials with clinical end points are required.

Introduction

The introduction in industrialised countries of highly active antiretroviral therapy—a combination of three drugs including either a protease inhibitor or a non-nucleoside analogue reverse transcriptase inhibitor (NNRTI) and two nucleoside analogue reverse transcriptase inhibitors (NRTIs)—led to a dramatic decline in morbidity and mortality among patients infected with HIV-1.¹⁻³ Many different combinations of highly active antiretroviral therapy regimens are available, some of which differ in toxicity, adverse events, their ability to suppress viral replication, the development of viral resistance, and patient adherence.⁴⁻⁷

No randomised clinical trials have compared the clinical effectiveness of protease inhibitor based and NNRTI based combination therapies. Thus it is unclear whether there are relevant differences between the regimens in preventing clinical progression to AIDS or death. In trials comparing highly active antiretroviral therapy regimens, the low rate of disease progression made it impractical to use clinical events as primary end points. Trials exclusively reporting surrogate endpoint data, however, have to be interpreted with caution.^{8,9}

We performed indirect comparisons between triple regimens based on protease inhibitors and NNRTIs by using clinical and surrogate endpoint data from randomised controlled trials comparing triple regimens with dual regimens.

Methods

Using Cochrane methods we searched Medline, the Cochrane controlled trials register, Aidstrial, and Aidsdrugs for randomised clinical trials of antiretroviral therapy in patients infected with HIV-1 published from January 1994 to December 2000.¹⁰ We also hand searched reference lists, reviews, and abstracts from major conferences and consulted the French Arcat Sida register, the European database on AIDS and HIV

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BMJ 2004;328:249-53



This is the abridged version of an article that was posted on
bmj.com on 23 January 2004: <http://bmj.com/cgi/doi/10.1136/bmj.37995.435787.A6>

infection, and the database of the US Community Programs for Clinical Research on AIDS. Finally, we contacted experts and pharmaceutical companies.

Inclusion criteria, data abstraction, and outcomes

We included randomised controlled studies published in any language if they reported on clinical end points and enrolled patients who were HIV-1 positive, aged 16 years or older, and had not received protease inhibitors or NNRTIs. We were interested in triple antiretroviral therapy compared with dual therapy based on recommended antiretroviral agents.^{11 12} Dual therapy was defined as a combination of two NRTIs and triple therapy as two NRTIs combined with a protease inhibitor or an NNRTI.

The primary outcome was progression to a new AIDS defining disease or death.¹³ Additional outcomes included the CD4 cell count, plasma HIV-1 RNA concentration, and the proportion of patients reaching plasma HIV-1 RNA concentrations of less than 500 copies/ml at the end of follow up. We assessed the methodological quality of trials on the basis of adequacy of concealment of patients' allocation to treatment group and blinding to placebo.¹⁴

Statistical analysis

Data on clinical progression and suppression of viral replication were based on intention to treat analysis. We calculated odds ratios with 95% confidence intervals, comparing the probability of clinical progression and the probability of reaching HIV-1 RNA concentrations below 500 copies/ml between patients receiving triple antiretroviral therapy and those receiving dual therapy.

We used random effects models to combine results on the odds ratio or weighted mean difference scales. The degree of between trial heterogeneity was measured by the additive between trial variance (τ^2). Publication bias was assessed by funnel plot. Crude and adjusted indirect comparisons were performed by fitting random effects meta-regression models. Variables entered in the model are detailed on bmj.com.

Results

We identified 14 trials that met our inclusion criteria (see bmj.com). The 14 trials totalled 6785 patients (table). Nine trials described adequate concealment of allocation and 12 used placebos to blind patients and caregivers.

Characteristics of 14 randomised controlled trials comparing protease inhibitor based triple therapy and non-nucleoside analogue reverse transcriptase inhibitor (NNRTI) based triple regimens with dual therapy

Trials (see bmj.com for references)	No of patients	Median age (years)	No (%) male	No (%) with AIDS	Median CD4 cell counts/ μ l*	Median HIV RNA concentration (\log_{10} copies/ml)*	Follow up (weeks)	Drug comparison
Protease inhibitor based regimen:								
AIDS Clinical Trials Group 229, 1996	198	38	183 (92)	23 (11)	158	4.8	36-56	Saquinavir, zidovudine, and zalcitabine v zidovudine and zalcitabine
AIDS Clinical Trials Group 320, 1997	1156	39	NR	1156 (100)	87	5.0	38	Indinavir, zidovudine, and lamivudine v zidovudine and lamivudine
Merck 035, 1997	66	41	58 (88)	8 (13)	139	4.6	52	Indinavir, zidovudine, and lamivudine v zidovudine and lamivudine
RTV Study Group, 1998	1090	38	999 (92)	1090 (100)	20	5.4	26	Ritonavir and two NRTIs v two NRTIs
Merck 039, 1999	213	40	186 (87)	119 (56)	19	4.8	24	Indinavir, zidovudine, and lamivudine v zidovudine and lamivudine
Spanish Earth-1, 1999	66†	31	45 (68)	0	651	4.6	52	Ritonavir, stavudine, and lamivudine v stavudine and didanosine
PISCES, 2000	1897	34	1576 (83)	NR	210	5.1	80	Saquinavir, zidovudine, and zalcitabine v zidovudine and zalcitabine
NNRTI based regimen:								
AIDS Clinical Trials Group 241, 1996	398	38	318 (80)	66 (17)	137	6.4	48	Nevirapine, zidovudine, and didanosine v zidovudine and didanosine
AIDS Clinical Trials Group 193A, 1997	662	38	576 (87)	662 (100)	19	4.8	65	Nevirapine, zidovudine, and didanosine v zidovudine and didanosine
Study 0021 Pt 2, 1998	248	NR	NR	NR	358	4.4	52	Delavirdine, zidovudine, and lamivudine v zidovudine and lamivudine
INCAS, 1998	104†	38	97 (93)	0	388	4.4	52	Nevirapine, zidovudine, and didanosine v zidovudine and didanosine
ISS 047, 1999	68†	37	58 (85)	27 (40)	83	5.6	48	Nevirapine, zidovudine, and didanosine v zidovudine and didanosine
AIDS Clinical Trials Group 261, 1999	274	35	228 (83)	NR	289	4.4	48	Delavirdine, zidovudine, and didanosine v zidovudine and didanosine
Study 13C, 1999	345	36	226 (66)	225 (65)	210	4.9	52	Delavirdine, zidovudine, and one NRTI v zidovudine and one NRTI

NR=not reported. *Mean values used if median not available. †Patients naive to nucleoside analogue reverse transcriptase inhibitors.

Clinical progression

Clinical progression occurred in 445 of 3392 patients (13.1%) receiving triple therapy and 651 of 3393 (19.2%) patients receiving dual therapy (fig 1; combined odds ratio 0.65 (95% confidence interval 0.52 to 0.81)). Heterogeneity was evident between trials, with odds ratios ranging from 0.32 to 1.31 ($\tau^2 = 0.073$, test of heterogeneity $P = 0.090$).

In univariate meta-regression analysis, protease inhibitor based triple regimens showed larger treatment effects than those based on NNRTIs ($P < 0.0001$), triple regimens including didanosine showed smaller treatment effects than those without didanosine ($P < 0.0001$), and trials that enrolled a larger proportion of patients with AIDS tended to show larger differences in treatment effects between triple and dual regimens ($P = 0.067$). These variables were responsible for the between trial heterogeneity. We found little evidence for an association with other variables entered in the model, including length of follow up, year of publication of the trial, publication in full or as abstract only, median age of study populations at baseline, whether patients were NRTI naive or not, and CD4 cell count and viral load at baseline. Finally, there was little evidence that the censoring strategy (follow up censored at virological failure or not) or the quality of trials influenced results, and little evidence of funnel plot asymmetry.

When triple regimens were compared with dual regimens the odds ratio for clinical progression was 0.49 (0.41 to 0.58) for a protease inhibitor based regimen but 0.90 (0.71 to 1.15) for an NNRTI based regimen. The crude odds ratio from the indirect comparison was 0.54 (0.40 to 0.73). This changed little when adjusted for whether or not the regimen included didanosine, for the proportion of study participants with AIDS, or for both variables, although adjustments resulted in odds ratios with wide confidence intervals which included 1 (fig 2). When trials were excluded that examined saquinavir hard gel, which is no longer used, or the NNRTI delavirdine, which is not widely used, the protease inhibitor based triple regimens continued to show larger treatment effects than the NNRTI based regimens (0.54, 0.37 to 0.77).

Differences in CD4 cell count and plasma HIV-1 RNA concentration

Eleven studies could be included in the analysis of CD4 cell counts. Compared with dual regimens, triple regimens led to a superior CD4 cell response (pooled difference in CD4 cell count, 40 (19 to 60) cells/ μ l; see also bmj.com). An indirect comparison showed an additional increase of 25 (-17 to 68) CD4 cells/ μ l with protease inhibitor based regimens when compared with NNRTI based regimens. Triple therapy was also superior to dual therapy, resulting in an estimated additional reduction of HIV-1 RNA concentrations of 0.56 (0.92 to 0.19) log copies/ml. The odds ratio for achieving a viral load below 500 copies/ml with triple compared with dual therapy was 9.6 (4.4 to 21.0). Again, the indirect comparison showed an additional reduction of HIV RNA concentration of -0.59 (-1.32 to 0.15) log copies/ml with protease inhibitor regimens compared with NNRTI based regimens. The odds ratio for reaching an undetectable viral load was 6.0 (2.2 to 16.6).

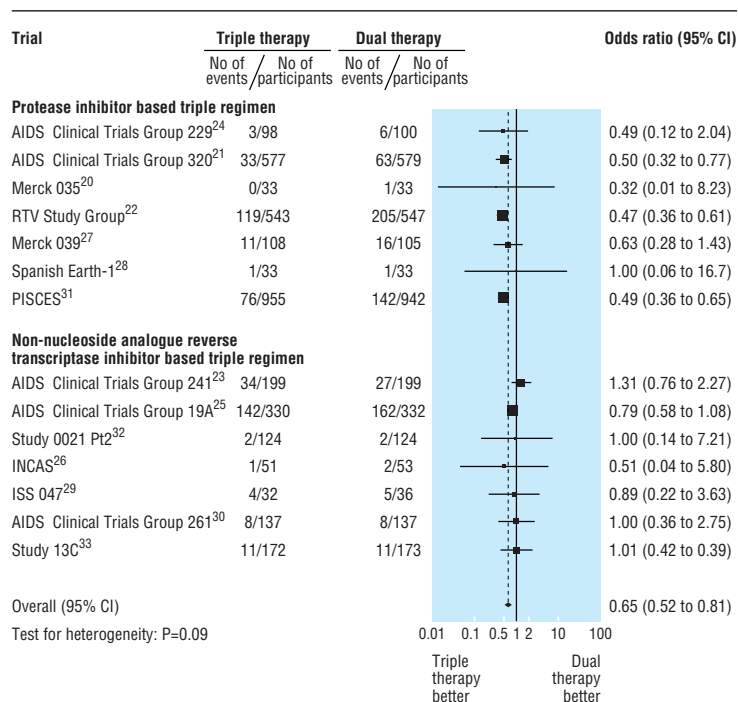


Fig 1 Meta-analysis of randomised controlled trials comparing effect of triple antiretroviral regimens with dual regimens on progression to AIDS or death, stratified by type of triple regimen

Discussion

Triple antiretroviral therapy is superior to dual therapy for preventing progression to AIDS or death in patients with advanced disease who have been exposed to NRTIs. Surprisingly, we found large variation between the results of the included trials. This was largely explained by the drug classes used in triple regimens: those containing protease inhibitors were clearly superior to dual regimens but this was not the case for triple regimens based on the NNRTIs nevirapine and delavirdine. Indirect comparisons indicated that the risk of clinical progression was reduced by 40-50% with protease inhibitor based regimens. In line with these findings, we found smaller increases in CD4 cell counts and less pronounced suppression of viral replication with the NNRTI based regimens.

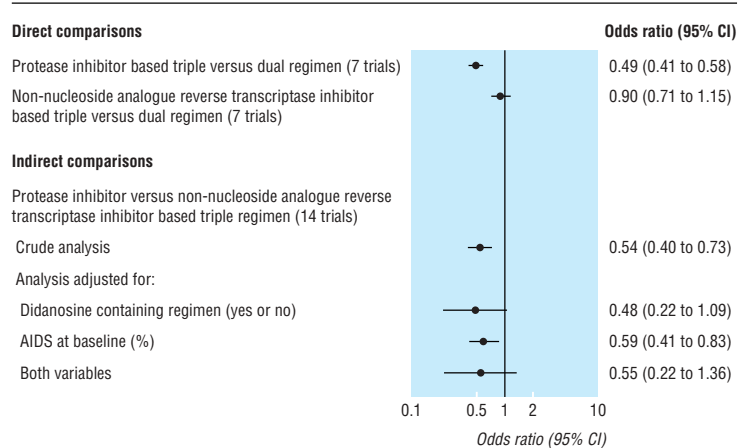


Fig 2 Comparisons from meta-analysis of randomised controlled trials comparing the effects of triple antiretroviral regimens with dual regimens on risk of progression to AIDS or death

What is already known on this topic

Randomised clinical trials have strongly supported triple antiretroviral regimens in HIV infected patients

No trials have compared the clinical effectiveness of protease inhibitor regimens with non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens

In the absence of such trials, indirect comparisons can provide useful information

What this study adds

Indirect comparisons suggest that triple regimens with protease inhibitors are superior to those with the NNRTIs nevirapine or delavirdine in patients with advanced disease who have used nucleoside reverse transcriptase inhibitors

In the absence of large trials directly comparing these regimens these results are relevant to current antiretroviral therapy, particularly in settings where resistance testing is not widely available

Strengths and limitations

No data from direct randomised comparisons of the clinical efficacy of different triple antiretroviral regimens exist. Our systematic review is based on 6785 patients, 1096 of whom progressed to AIDS or died, from trials comparing triple regimens with dual regimens. This represents a large evidence base, suitable for indirect comparisons of the clinical effectiveness of the antiretroviral regimens. Such comparisons were appropriate because the trials were of high methodological quality.

Our findings should, however, be interpreted with caution. Firstly, the finding of superior efficacy of protease inhibitor based regimens by indirect comparison is observational and therefore vulnerable to bias. Baseline characteristics of the participants were heterogeneous in both groups, with large variations in the proportion of patients with AIDS, the median CD4 cell count, and viral load. Furthermore, didanosine was more often used with NNRTIs than with protease inhibitors. When we adjusted for these differences in meta-regression models, the coefficients were not noticeably altered. We acknowledge that we could only adjust for information that was aggregated at the trial level. Individual patient data would have been preferable but were not available. Indirect comparisons adjusted at the aggregate level usually agree with direct comparisons.¹⁵ Finally, the smaller gains in CD4 cell counts and less pronounced suppression of viral replication with NNRTI based triple regimens support the finding of higher progression rates.

Our results are limited to the regimens and patient populations of the included studies—for example, the NNRTI efavirenz was not included in the triple regimens. The trials involving efavirenz that we identified did not assess clinical end points and had to be excluded. Several observational cohort studies have shown efavirenz to be more efficacious than nevirapine.^{16–18} However, the recent 2NN trial, which directly compared these two drugs in antiretroviral naive patients showed that they did not differ in their ability to suppress viral replication.¹⁹ Furthermore, most of the patients enrolled in the trials in our meta-analysis used

NRTIs. Thus, it is not possible to extrapolate these results to HIV-1 infected patients who have never used antiretroviral drugs, a population in which NNRTI based regimens are widely used. It may be postulated that due to cross resistance, patients who have previously undergone prolonged therapy with NRTIs would be resistant to all drugs in the NRTI class. In this situation, a regimen containing one protease inhibitor and two NRTIs could be more effective than a regimen based on one NNRTI and two NRTIs because the genetic barrier to resistance is greater with protease inhibitors.²⁰

Our results provide important information for clinical practice, and may be especially relevant for doctors working in countries where resistance testing is not generally available. In these countries, patients tend to be at an advanced stage when starting therapy and, particularly in urban settings, a proportion will have been exposed to NRTI monotherapy or dual therapy.²¹

Contributors: See bmj.com

Funding: None.

Competing interests: YY has received travel grants from various pharmaceutical companies including Aventis, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmith-Kline, Pfizer, Roche, and Schering Plough. He has received honorariums for presentation at workshops and consultancy honorariums from Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Pfizer. ME has received travel grants, grants, or honorariums from Boehringer Ingelheim, Bristol-Myers-Squibb, and GlaxoSmithKline. YM has received travel grants, grants, or honorariums from Abbott, Aventis, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp and Dohme, Pfizer, Roche, and Schering. GC has received consultancy honorariums from Aventis, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmith-Kline, and Roche.

Ethical approval: None required.

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doi 10.1136/bmj.37995.435787.A6

Commentary: Indirect comparisons: a novel approach to assessing the effect of anti-HIV drugs

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The need to evaluate rapidly and provide access to anti-HIV drugs led, in 1997, to an expedited drug approval process, based on short term trials using viral load and CD4 cell counts as surrogate end points for clinical AIDS. The evidence for efficacy of many drugs is therefore based solely on trials using such end points, but it is useful to evaluate studies using clinical end points where available.

Yazdanpanah and coworkers used an indirect comparison of clinical outcomes from randomised controlled trials to compare the effects of drugs from either the protease inhibitor or the non-nucleoside reverse transcriptase inhibitor (NNRTI) class with two nucleoside reverse transcriptase inhibitors (nucleosides).¹ This approach introduces a novel concept to improve further our understanding of the relative efficacy of the two classes. This review suggests a better efficacy of the protease inhibitors than the NNRTIs.

It is important to understand the context of the results to draw conclusions relevant to today. Most of the randomised controlled trials focused on viral end points and were not designed to capture clinical events after virological failure.² Also, many of the drugs from the NNRTI and protease inhibitor classes are considered obsolete, although the NNRTI drug most represented, nevirapine, is still widely used. Furthermore, most trials were based on people with previous exposure to nucleosides and thus likely to harbour virus with resistance to the nucleosides at enrolment. Since the genetic barrier for NNRTIs is lower than for protease inhibitors (with a single nucleotide mutation sufficient to create resistance), it would be predicted that resistance would develop more rapidly with NNRTI based regimens than with protease inhibitor based regimens in this situation, and hence that the clinical outcome would be poorer. The review seems to confirm this prediction, finding little beneficial effect of NNRTIs at all. Importantly, the results for viral load and clinical outcomes are broadly consistent with a better effect of protease inhibitors. In patients starting anti-HIV therapy for the first time, however, several randomised controlled trials with surrogate end points have directly shown that the efficacy of NNRTIs is

comparable and perhaps even superior to protease inhibitors.³⁻⁵

None the less, there are situations in which the findings of Yazdanpanah and coworkers are relevant to today.¹ Frequently, exclusive resistance to nucleosides is seen at failure of current regimens, including triple nucleoside regimens. Furthermore, the WHO has recently launched its 3 by 5 motto of providing anti-HIV therapy to 3 million people by the end of 2005. Hopefully, the therapy will be state of the art, but some may receive inferior regimens of 1-2 nucleosides, increasing the number of patients with resistance to these drugs. It will be critical to start randomised controlled trials with clinical outcomes to establish a rational order of utilisation of the available anti-HIV drugs in this situation. Hopefully, the WHO or other organisations will ensure that this critical knowledge is generated. Yazdanpanah and coworkers provide a strong rationale that this is important.¹

Contributors: JDL wrote the commentary, which was critically revised by ANP.

Funding: None.

Competing interests: JDL has received grant support and fees from Abbott, Bristol-Myers-Squibb, Roche, Boehringer Ingelheims, Pfizer, Merck, and GlaxoSmithKline. ANP has received consultancy fees, grants or funds for meetings from Abbott, Bristol-Myers-Squibb, Roche, Boehringer Ingelheim, and GlaxoSmithKline.

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