Antiretroviral Therapy for HIV Infection in Patients Naive to Prior Treatment: a Systematic Review of Effectiveness and Cost-Effectiveness

A West Midlands Health Technology Assessment Collaboration Report

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West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

About InterTASC

WMHTAC is a member of InterTASC which is a national collaboration with three other units who do rapid reviews: the Trent Working Group on Acute Purchasing; the Wessex Institute for Health Research and Development; York Centre for Reviews and Dissemination. The aim of InterTASC is to share the work on reviewing the effectiveness and cost-effectiveness of health care interventions in order to avoid unnecessary duplication and improve the peer reviewing and quality control of reports.

Acknowledgements

Rachel Jordan was the main reviewer and carried out the searches, data extraction, analysis of the effectiveness section and wrote the report. Lisa Gold (co-reviewer and health economist) assisted with the searches, data extraction and quality assessment, and reviewed the economic literature. Chris Hyde (Senior Reviewer) directed the project, wrote the costs section, made detailed comments on the text and results and scrutinised the original papers to resolve problems. Carole Cummins gave statistical input to the meta-analysis and meta-regression stages and commented on the text. Thanks also to Jeremy Hawker, Ruth Lockley and Sue Drake for their advice at the protocol stage, and to Matthias Egger, Sarah Walker, Abdel Babiker, Jeremy Hawker, Paul Aveyard and Sue Simpson for their comments on the final draft.

Conflicts of Interest

None.

West Midlands Regional Evaluation Panel Recommendation:

The recommendation for the use of Antiretroviral therapy for HIV infection in patients naive to prior treatment: a systematic review of effectiveness and cost-effectiveness:

Evidence category II: Supported

Good quality trials are available in this fast moving field, although many are short-term in nature and preclude proper evaluation of clinical outcomes. This review collates and evaluates the evidence underpinning the policy of providing triple therapy over double and monotherapy. The evidence is consistent with triple therapy being more effective, which should reassure policy makers and clinicians. New treatments and combinations of treatments are rapidly available for HIV patients, and it will be necessary for researchers to regularly review the field to keep pace with new developments and to evaluate whether greater numbers of drugs in combination are justified. Cost-effectiveness studies will always be difficult to interpret if short term data are used.

Anticipated Expiry Date

- The searches were completed to end 1999
- The report was completed in June 2000
- An updated paper of the clinical effectiveness was published in the BMJ in 2002: **Jordan R. Gold L. Cummins C. Hyde C. Systematic review and meta-analysis of evidence for increasing numbers of drugs in antiretroviral combination therapy. BMJ. 324(7340):757, 2002 Mar 30.**

Research and licensing of new treatments for HIV moves extremely rapidly and therefore research publications are quickly out of date. This review, however, provides solid evidence that the treatment policies were justified in moving from mono- to double- to triple therapy as the standard firstline treatment for HIV-positive previously untreated patients.

Contents

Executive Summary

- **Background**

Uncertainties about the effectiveness of multiple combinations of antiretroviral therapy for the treatment of HIV, combined with escalating costs prompted West Midlands healthcare commissioners to request a systematic review of the effectiveness and cost-effectiveness of antiretroviral therapy. Comparisons between and within combinations of the same number of drugs (monotherapy, double therapy, triple therapy and quadruple therapy) were examined in HIV positive patients with no prior treatment.

- **Methods**

Randomised controlled trials of any antiretroviral therapy compared with placebo or other antiretroviral therapy, in HIV positive patients naïve to previous therapy, were sought via MEDLINE, EMBASE, Cochrane CTR, CINAHL, PSYCHLIT, Healthstar, NHS EED and OHE HEED (all to the end of 1999). Pharmaceutical companies and experts were also contacted for published and unpublished trials, and citation lists studied. No restriction was placed on language. The quality of each paper was assessed using a standard checklist and data extraction performed by two independent reviewers. Meta-analysis was performed in order to produce pooled estimates for each of four outcomes (CD4 count, viral load, disease progression and death, and drug-related adverse events). Meta-regression techniques were used to explore any heterogeneity. The economic literature was reviewed for cost-efectiveness information.

- **Effectiveness Results**

81 papers were included which referred to 47 different trials. In general, the quality of the studies was good – most were double-blind and at least a third gave information about satisfactory randomisation allocation. The largest proportion of patients were asymptomatic, with baseline CD4 counts ranging from 83 to 660 cells per μl. Most patients were naïve to prior therapy. The outcomes with the most information were CD4 count, viral load, disease progression and death and drug-related adverse events. There was very limited information on health-related quality of life, resource use or costs.

- **Effectiveness of increasing numbers of drugs**

For CD4 count, most of the individual studies showed effects favouring the larger numbers of drugs. Combined estimates suggested that each extra drug improved outcome by approximately 45-60 cells per μl, although there was frequent unexplained heterogeneity.

For viral load, all trials showed effects favouring the the larger numbers of drugs, and the combined estimates showed a reduction in viral load with each extra drug of between 0.56 and 0.66 log copies per ml. However, again there was significant unexplained heterogeneity at each comparison level.

For disease progression/death, most mono and double comparisons showed improvement with the extra drug (OR 0.6-0.7), although again there was significant heterogeneity, in part explained by the length of the trial. Triple therapy versus double therapy data was difficult to interpret.

For drug-related adverse events, monotherapy was worse than placebo, although double therapy was similar to monotherapy.

- **Effectiveness of specific combinations**

Data were very limited, with many possible comparisons unavailable. Where effectiveness data were available, the results were inconsistent and preclude any firm conclusions about the relative effectiveness of different combinations.

Rates of withdrawals due to adverse effects were clearer, demonstrating no difference between combinations of the same number of drugs.

- **Economic evaluation**

None of the included randomised controlled trials (RCTs) included an economic evaluation. Other economic studies available were based on treatment-experienced or mixtures of naïve and experienced patients, and used data from RCTs, observational studies and models. The quality of economic evaluations has improved over time, but all have the common problem of projecting long term outcomes with only short term data. A tentative range of cost-effectiveness might be £4,000 to £20,000 per life-year saved.

- **Conclusions**

All the disease outcomes (CD4 count, viral load and disease progression/death) are consistent with triple therapy > double therapy > monotherapy > no treatment (data for quadruple therapy was too limited to conclude this). Commissioners should be reassured that treatment policy has been justified so far, but should be aware that more evidence is needed to examine the effectiveness of individual drug combinations and additions before endorsing larger numbers of drugs. Cost-effectiveness studies will always be difficult to interpret if short term data are used. High quality longer term cohort studies will be required to evaluate life-time costs and effects.

Abbreviations

HIV	Human immunodeficiency virus
AIDS	Acquired Immune Deficiency Syndrome
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor
Plasma VL	Plasma Viral Load (quantity of HIV-1 RNA – copies per ml)
ZDV	Zidovudine
Did	Didanosine
Zalc	Zalcitabine
Lam	Lamivudine
Saq	Saquinavir
Rit	Ritonavir
Aba	Abacavir
Nev	Nevirapine
Del	Delavirdine
Ind	Indinavir
Efa	Efavirenz
Lov	Loviride
Ate	Atevirdine
Amp	Amprenavir
P	Placebo

1 Rationale and aims of the project

At present there is no cure for HIV infection. Therapy is based on delaying the progression of the disease, and treating any opportunistic infections which arise. The mainstay of therapy are the antiretroviral drugs, the number of which, and the combinations in which they are given, has increased rapidly over the last five years. The cost of triple therapy can be up to four times the cost of monotherapy with zidovudine and further quadruple or higher combinations will correspondingly increase the HIV drugs budget. It is not clear what advantages in clinical effectiveness there are by each increase in combination (although it is generally accepted that triple therapy does provide improvements over previous double and monotherapy), and whether the benefits in the long term outweigh the difficulties, adverse effects and costs of treatment.

The issue has been raised in the West Midlands as a matter of concern to commissioners who need to decide what, and how much, to fund on HIV treatments when they have many other competing interests, both within and outside HIV-allocated budgets. The same issues will be relevant throughout the UK and also internationally. Commissioners need to know firstly, whether the treatment for HIV is effective, and secondly, whether it is cost-effective. This review addresses these issues.

1.1 Aims

The aim of this study is to produce a systematic review with a meta-analysis of the effectiveness of antiretroviral therapy in HIV positive patients who have not had prior treatment, and also provide an evaluation of the available economic analyses. Patients naïve to prior therapy are selected in order to avoid potential dilution of the effects in patients with established drug-resistance.

2 Background

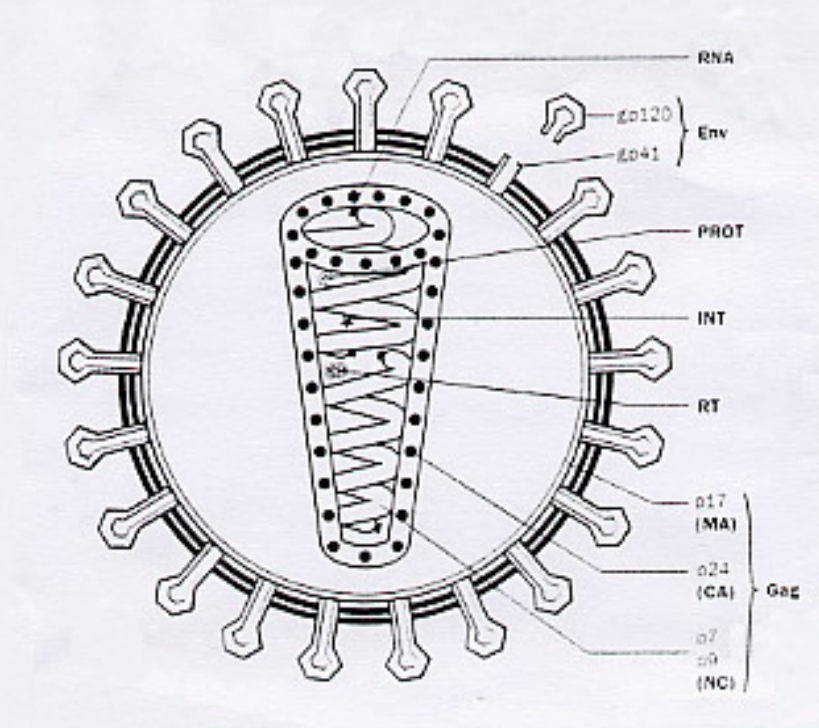
2.1 Pathogenesis, aetiology, natural history and prognosis of HIV

2.1.1 HIV – basic structure

HIV viruses (HIV-1 and HIV-2) are retroviruses, distinguished primarily by the diploid single stranded RNA – the genetic material of the virus. HIV virions contain a virus capsid that consists of the major capsid protein (P24), the nucleocapsid protein (P7/P9), the single stranded RNA and the viral enzymes reverse transcriptase, integrase and protease. The viral capsid is surrounded by a matrix protein (P17) and the virion envelope (a lipid bilayer with associated proteins gp120 and gp41)[1] (figure 1). The HIV-1 virus is more common, particularly in the Western world[2] and will be the focus of this review. HIV-1 has several variants but they are usually referred to collectively as HIV-1.

Figure 1 - Schematic diagram of an HIV virion

Source: Barre-Sinoussi, 1996[1]



HIV – host target

HIV viruses target the cells of the immune system, specifically T cells with CD4 receptors, macrophages and dendritic cells [3]. The HIV envelope protein binds to the host cell[1; 4], fuses with the cell membrane and enters the cell. Once inside the host cell cytoplasm, the *reverse transcriptase* enzyme converts the virus single stranded RNA template to double stranded DNA. Transcription of new viral RNA using the host cell mechanisms followed by the viral proteins produces new viral particles that are assembled and released into the plasma. The infected T cells are killed by the HIV virus. This reduces the pool of both memory T cells and naïve T cells, reducing the ability of the immune system to respond to further HIV infection or other infections[1].

2.1.2 The consequences of HIV infection

As the HIV infection progresses and the immune system becomes depleted because of the declining CD4 T cell count (and later the CD8 cells, B lymphocytes and Natural Killer cells), unusual opportunistic infections and diseases such as *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus (CMV), Kaposi's Sarcoma and Oral Hairy Leukoplakia occur until eventually patients reach a point where their condition is defined as AIDS (Acquired Immune Deficiency Syndrome). The Centers for Disease Control and Prevention (CDC) in the US [5] define the stages of HIV infection by letter and number. The letters (A-C) represent the clinical categories of disease by symptoms, and the numbers (1 – 3) represent the CD4 count. Table 1 illustrates the classification. Table 2 lists the AIDS indicator conditions in category C.

Table 1 - HIV clinical categories **Source: US CDC[5]**

CD4 T-cell categories	Clinical Categories		
	A. Asymptomatic HIV infection Persistent generalised lymphadenopthy (PGL) Acute (primary) HIV infection with accompanying illness (seroconversion illness) or history of acute HIV infection	B. Symptomatic conditions not included in (C) and are: Attributed to HIV infection or indicative of a defect in cell-mediated immunity Or Conditions considered to have clinical course or to require management that is complicated by HIV infection Eg oral hairy leukoplakia, peripheral neuropathy	C. AIDS indicator conditions (see table 2)
1. 500 or above	A1	B1	C1
2. 200 to 499	A2	B2	C2
3. Less than 200	A3	B3	C3

Table 2 - AIDS indicator conditions **Source: US CDC[5]**

AIDS Indicator Conditions	
Candida in the oesophagus, trachea, bronchi or lungs	Kaposi's sarcoma
Invasive cervical cancer	Burkitt's, immunoblastic or primary brain lymphoma
Coccidiodomycosis	Widespread *Mycobacterium avium intracellulare* (MAI), *M kansaii* or other species
Cryptococcus outside the lungs	*Pneumocystis carinii* pneumonia
Cryptosporidiosis with diarrhoea lasting for more than one month	Recurrent bacterial pneumonia
CMV disease outside the liver, spleen or lymphnodes	Progressive multifocal leukoencephalopathy
Herpes simplex virus causing prolonged skin problems or involving the lungs or oesophagus	Recurrent *Salmonella* scepticaemia
HIV-related encephalopathy	Toxoplasmosis of the brain
Chronic intestinal isopsoriasis lasting longer than one month	HIV wasting syndrome

2.1.3 Testing and monitoring in HIV infection

The initial test for HIV positivity is a serum test for HIV specific IgG antibodies which are produced 2-3 weeks after initial infection[6].

The progression of HIV infection is commonly measured by "surrogate outcomes": CD4 count (a marker of progression of immunodeficiency) and plasma viral load (the number of virus particles detected in the blood). CD4 count is measured by standard flow cytometry, and viral load is usually measured in the UK by molecular techniques known as PCR (polymerase chain reaction) assays[7], with lower limit sensitivities ranging from 20-500 HIV-RNA copies per ml[7; 8].

The change in level of viral load detectability over time and the variety of assay used in different trials has implications for assessing and comparing the effectiveness of regimens which use plasma viral load as an outcome.

2.2 Epidemiology of HIV

The rates of HIV infection vary enormously across the World (table 3), with the countries of sub-Saharan Africa having the highest rates (on average in this region 7% of the adults aged 15-49 are HIV positive, although in some countries, such as Botswana and Zimbabwe, the estimates are as high as 25%.)[9]. Western countries such as Western Europe and the USA

have a HIV prevalence rates of less than 1%, with the UK estimated at 0.09%[9]. The highest prevalence is in London at 0.2% which is approximately 15 times higher than the rest of the UK (based on unlinked anonymous testing in 1998)[10]. In the West Midlands, the prevalence is approximately 0.01%[11], which is similar to other areas outside London. Currently (as of May 2000), there are approximately 800 HIV positive people named and known to be living in the West Midlands (Personal Communication. Rehman, Y.)

The time lag between infection and onset of symptoms[9], the fact that people must give consent for named tests, the adverse social implications of having a test for HIV, and the lack of surveillance methods, (particularly in developing countries) mean that the prevalence and incidence data may not be totally accurate.

Table 3 - Prevalence of HIV positive adults (aged 15-49) in selected regions (end 1997)

	Total number of adults aged 15-49 (thousands)	*Number of HIV positive adults aged 15-49*	*Prevalence of HIV positive adults (%)*
Western Europe	201,131	480,000	0.23
France	29,347	110,000	0.37
Germany	41,035	35,000	0.08
Spain	20,893	120,000	0.57
UK	28,223	25,000	0.09
North Africa & Middle East	164,259	200,000	0.13
Sub-Saharan Africa	268,439	20,000,000	7.41
Botswana	743	190,000	25.1
Gambia	559	13,000	2.24
Malawi	4,474	670,000	14.92
Rwanda	2,710	350,000	12.75
South Africa	21,717	2,800,000	12.91
Zimbabwe	5,560	1,400,000	25.84
South and South-East Asia	954,510	5,700,000	0.61
Afghanistan	10,777	<100	<0.005
Cambodia	4,994	120,000	2.40
India	494,756	4,100,000	0.82
Thailand	34,433	770,000	2.23
Eastern Europe & Central Asia	193,385	180,000	0.09
East Asia & Pacific	814,557	420,000	0.05
Australia & New Zealand	11,450	12,000	0.11
North America	156,277	850,000	0.55
Canada	15,923	43,000	0.33
USA	140,354	810,000	0.76
Caribbean	16,368	300,000	1.82
Latin America	241,482	1,300,000	0.52
Total	3,035,425	29,400,000	0.97

Source: UNAIDS & WHO, 1998[9].

In the UK, Western Europe, North America and Latin America, spread was initially mainly via sex between men and through infected needles shared by injecting drug users[9]. However, in the UK, the rates of infections due to transmission by the heterosexual route are rising towards that of the homosexual route[12]. Rates are highest in communities with higher numbers of intravenous drug-users, homosexual men and immigrants from Africa.

In many industrialised countries, regardless of the HIV infection rate, the numbers of AIDS cases are falling. In Western Europe, new AIDS cases fell from 23,954 in 1995 to 14,874 in 1997, a 38% drop[9]. This is partly due to prevention methods promoted by the gay community and also targeted at young adults, but is probably due most of all to new combination antiretroviral therapies which postpone the development of AIDS in HIV positive people[9].

2.2.1 Prognosis

Without treatment, the median length of survival from infection to AIDS is ten to eleven years, but once AIDS has been diagnosed, median survival is two to three years[4]. Although it is too early to quantify the increase in survival due to antiretroviral drug therapy, triple combination therapy has had a substantial impact on disease progression of the virus and survival rates[13; 14].

2.3 Impact on Public Health

HIV/AIDS in the UK has not reached the epidemic proportions first projected in the early 1980s. However, it is an important disease as it is spread often unknowingly, and there is as yet no cure. Treatment of HIV to delay progression to AIDS has important implications for HIV positive patients, extending their active lives, and for the health service by potentially delaying or decreasing the burden of opportunistic infections and subsequent hospitalisation and treatment. The treatment of HIV positive patients also has wider implications. A benefit is the reduced rate of infections transmitted from mother to child[2] and the improved lives for children of HIV positive parents whose parents will be alive for longer. A negative effect is the potentially increased chance of transmission to uninfected people as HIV patients live longer and are sexually active for longer. However, treatment with antiretroviral drugs is expensive, and, as the number of drugs used in combination per patient increases, is becoming more expensive. It is unclear whether, in the long term, the benefits of antiretroviral therapy for HIV infection will outweigh the costs. There are many factors to consider, such as drug costs, reduced health care resource use due to improved health-related quality of life (HRQL), side-effects of treatment, disease progression and final effect on life expectancy. These aspects will be considered throughout the review, particularly with reference to the economic evaluations.

3 Treatment of HIV

3.1 General rationale

At present, there is no cure for HIV infection, and although recent treatment strategies have achieved undetectable plasma viral loads[15], it is increasingly unlikely that the HIV virus can be eliminated entirely from an infected individual[15-17]. There are candidate vaccines in trials[18; 19], but the main strategy of treatment is to reduce the speed of disease progression and to treat any opportunistic infections that arise. A class of drugs, known as antiretroviral drugs, are the mainstay of therapy, and act to reduce disease progression and immune deficiency by interfering with the life-cycle of the HIV virus.

3.2 Antiretroviral drug therapy

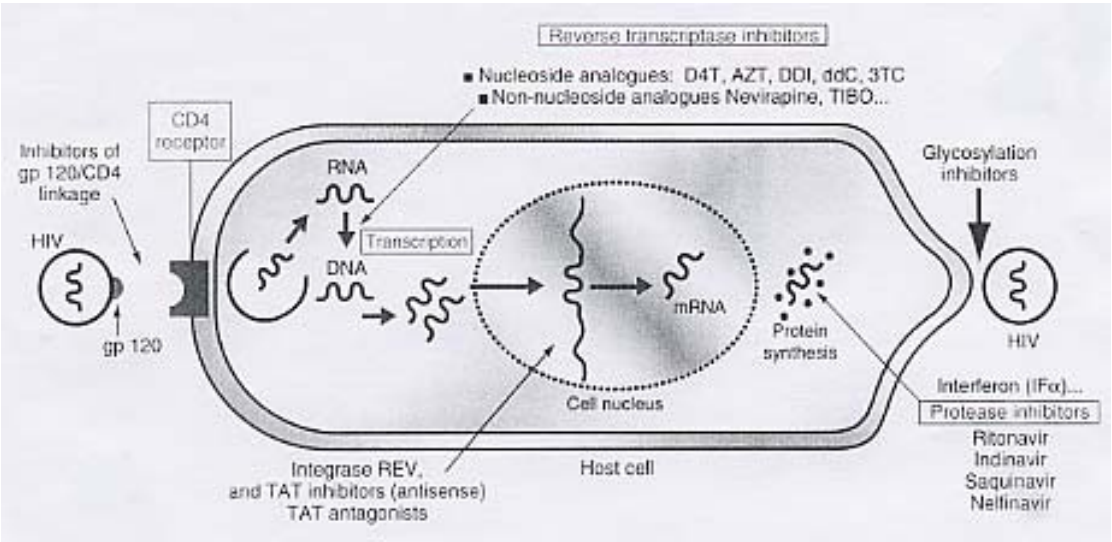
3.2.1 Mechanism of action

Figure 2 illustrates the life cycle of the HIV virus and the stages where there is potential for attacking the virus and halting its lifecycle. Opportunities for antiviral action occur by:[20]

- Preventing the attachment of virus to the cell
- Inhibiting reverse transcriptase (the enzyme which creates DNA from viral RNA)
- Inhibition of Rnase H, which degrades viral RNA after viral DNA has been synthesised
- Inhibition of viral integrase, which is used to integrate viral DNA into the cell's DNA
- Inhibition of expression of the HIV gene once it is integrated into the host-cell DNA (including transcription of more viral RNA and translation of viral proteins)
- Inhibition of processing and post-translational modification of protein products of the virus.

Figure 2 - Schematic diagram of an HIV infected cell and the opportunities for drug intervention

Source: "Guide to HIV infection and questions and answers on D4T" Bristol-Myers Squibb



The antiviral drugs currently licensed for treating HIV are from only two of the above categories; the reverse transcriptase inhibitors and the protease inhibitors (PI). Other potential anti-HIV strategies include the integrase inhibitors, anti-sense nucleotides, fusion inhibitors, zinc finger inhibitors, budding inhibitors and gene therapy[20 21]. A list of the licensed drugs, their usual dose and regimen and their approximate current weekly costs is given in table 4.

Table 4 - Anti-retroviral drugs currently available (licensed by FDA) [22-25]

Drug name	*Company Name*	*Normal dose and number of tablets*	*Cost*	*Cost per week (standard dose)*
Nucleoside reverse transcriptase inhibitors				
Lamivudine (3TC, Epivir)	Glaxo Wellcome	One 150mg tablet, twice a day without food	60 x 150mg = £163.59	£38.17 (7 x 2 x 150mg)
Zidovudine (ZDV, AZT, Retrovir)	Glaxo Wellcome	One 300mg tablet or one 250mg capsule twice a day before meals	40 x 250mg capsule = £119.33	£41.77 (7 x 2 x 250mg)
Zalcitabine (ddC, Hivid)	Roche	One 0.75mg tablet three times a day on an empty stomach	100 x 0.75mg = £151.57	£31.83 (7 x 3 x 0.75mg)
Didanosine (ddI, Videx)	Bristol Myers	Over 60kg – two 100mg tablets twice a day, or Under 60kg – 125mg twice a day on an empty stomach Can be taken once a day (Also a sachet format – 500 (334) mg per day)	60 x 100mg = £88.00	£41.07 (7 x 2 x 2 x 100mg)
Stavudine (d4T, Zerit)	Bristol Myers	One capsule twice a day (Over 60kg – 40mg; under 60kg – 30mg) 1 hour before food	56 x 40mg = £171.98	£43.00 (7 x 2 x 40mg)
Abacavir (1592U89, Ziagen)	Glaxo Wellcome	One 300mg tablet or 15ml twice daily	60 x 300mg = £238.50	£55.65 (7 x 2 x 300mg)
Non-nucleoside reverse transcriptase inhibitors				
Nevarapine (Viramune)	Boehringer Ingelheim	One 200mg tablet twice a day	60 x 200mg = £168.00	£39.20 (7 x 2 x 200mg)
Efavirenz (EFV, DMP 266, Sustiva)	DuPont	Three 200mg capsules once a day, at night.	90 x 200mg = £224.09	£52.29 (7 x 3 x 200mg)
Delavirdine (DLV, Rescriptor)*	Pharmacia & Upjohn	Four 100mg tablets three times a day.	No information available	No information available
Protease Inhibitors				
Indinavir (Crixivan)	MSD	Two 400mg capsules three times a day, 1 hour before and 2 hours after food. Drink at least 1.5 litres of fluids per day.	180 x 400mg = £217.81	£50.82 (7 x 6 x 400mg)
Nelfinavir (Viracept)	Roche	Three 250mg tablets three times a day with food	270 x 250mg = £289.23	£67.49 (7 x 9 x 250mg)
Ritonavir (Norvir)	Abbott	Six 100mg capsules twice a day	336 x 100mg = £377.39	£94.35 (7 x 2 x 6 x 100mg)
Saquinavir hard gel (Invirase)	Roche	Three 200mg capsules three times a day with a balanced meal	270 x 200mg = £289.23	£67.49 (7 x 3 x 3 x 200mg)
Saquinavir soft gel (Fortovase)	Roche	Six 200mg capsules three times a day with food	180 x 200mg = £104.34	£73.04 (7 x 3 x 6 x200mg)
Amprenavir (APV, 141W94, Agenerase)*	Glaxo Wellcome	1200mg capsules twice a day	No information available	No information available

*Not yet licensed in UK

3.2.2 Reverse transcriptase inhibitors

Currently there are two classes of drugs which inhibit the reverse transcriptase enzyme; the nucleoside analogue reverse transcriptase inhibitors (NRTIs), and the non-nucleoside reverse transcriptase inhibitors (NNRTIs). The *nucleoside* analogue reverse transcriptase inhibitors, once phosphorylated inside the cell, resemble the nucleotides which form human DNA, although they lack a hydroxyl group. They disrupt the construction of DNA by the enzyme reverse transcriptase in cells infected with HIV[20]. Zidovudine (AZT), a NRTI, was the first drug approved for use to treat HIV[20], and has been the mainstay of treatment since then. There are now several other drugs in this category (see table 4), but all NRTIs have limitations due to toxicity[16], for example, risk of neuropathy, pancreatitis and gastrointestinal disturbances, hepatitis and resistance, and cross-resistance within the group, which leads to lack of long-term efficacy.

Non-nucleoside reverse transcriptase inhibitors inhibit the activity of reverse transcriptase by binding to a hydrophobic pocket in the enzyme once it is complexed with the DNA[20]. The most common adverse effect of NNRTIs is hypersensitivity, particularly rash and hepatic enzyme elevations, although these are usually self-limiting[16; 22]. Cross-resistance within the group is very common[16].

Other reverse transcriptase inhibitors in development include the nucleotide analogues which do not require phosphorylation, and the ribonucleotide reductase inhibitors.

3.2.3 Protease Inhibitors

Protease inhibitors (PIs) inhibit the HIV proteinase enzyme, preventing the cleavage of protein precursors that form proteins crucial for viral replication, including the protease itself and reverse transcriptase, integrase and structural proteins. HIV then becomes non-infectious [20]. There are five agents approved for use, and all have limitations of toxicity (although often mild) [16; 24] (for example, nausea, diarrhoea and vomiting, paraesthesia), tolerance and resistance[20]. There is concern about the long-term use of protease inhibitors as they have been associated with severe lipodystrophy and lipid abnormalities[16], although this is not proven to be due exclusively to protease inhibitors[24]. Protease inhibitors have been used in several two-drug combinations to improve their bioavailabilityand reduce the doses of individual drugs[16]; the most well-studied combination is ritonavir and saquinavir.

3.2.4 Combination therapy

Monotherapy with zidovudine was the only treatment available until the early nineties. However, in order to improve efficacy, reduce the chances of resistance (and so increase survival) and minimise side effects by reducing the doses of each drug, dual therapy with two NRTIs was recommended in 1996[26] followed by triple combination therapy (which might include a combination of the three types of licensed drugs). Potent combinations of three or more antiretroviral drugs are commonly known as Highly Active Antiretroviral Therapy or HAART, and are expected to reduce plasma HIV-1 RNA levels below the limit of detection[16].
Larger combinations of drugs (Mega-HAART) are also being tested.

3.2.5 Choosing a treatment regimen

For HIV positive patients, initial antiretroviral combination therapy must be chosen very carefully in order to take into consideration the complex regimes that may be involved, drug interactions, tolerability of side effects and previous anti-retroviral treatment (which may

have produced both resistance to the same drug and cross resistance to other drugs of a similar class), and commitment to long-term therapy [16; 17]. Current US guidelines[27] advocate early aggressive therapy, although these recommendations are based on scientific rationale rather than evidence from clinical trials. There may be disadvantages to early aggressive therapy – compliance is difficult because of the side effect profile[16; 17] and complicated dosage regimens, particularly in asymptomatic patients. Poor compliance would increase the potential for resistance and cross resistance and limit future treatment options[16]. It is not known whether there is increased benefit from starting therapy earlier rather than later, or with a more or a less aggressive regime. UK guidelines take a more cautious approach[24], but are now closer to the US guidelines than they were previously[28]. Table 5 summarises the current UK guidelines.

Table 5 - Initiation of antiretroviral therapy in HIV: 1999 UK guidelines[24]

	When to start treatment	What treatment to start with
Primary HIV infection	If treatment considered, start as soon as possible	
Asymptomatic HIV infection		
CD4 > 500 cells/μl Any viral load	Defer treatment	
CD4 count 350-500 cells/μl Viral load <30,000 copies/ml	Defer treatment	2 NRTIs + PI 2 NRTIs + 2 PIs 2 NRTIs + NNRTI
CD4 count 350-500 cells/μl Viral load >30,000 copies/ml	Consider treatment or defer and monitor at least 3-monthly	3 NRTIs (under evaluation)
CD4 count 0-350 cells/μl Any viral load	Treat	
Symptomatic HIV infection	Treat	

The disadvantages of PI containing regimens are that they are demanding, unforgiving regimens, there is a possibility of major long term disturbances of fat metabolism and there is an increased risk of bleeding in haemophiliacs[28]. The disadvantages of NNRTI-containing regimens are that the potential for resistance is higher, and there is little experience of their effectiveness in late disease. However, NNRTI-containing regimens have much easier administration and no known major long-term toxicities[28]. Experience with 3 NRTIs is limited.

3.3 Treatment issues

Choosing the most suitable initial combination of antiretroviral drugs for HIV patients is only one of several questions that clinicians need to explore. Current unresolved issues include [29]:

- When is the optimum time to initiate therapy?[30] There is a lack of information on the long term effects of early, aggressive therapy. Many studies are short-term, with the effects of treatment measured using surrogate endpoints, for example, change in viral load or CD4 count. It is difficult to predict actual clinical effect from these imperfect proxy markers.

- When therapy fails, when to change treatment and how to decide which "salvage" therapy will be appropriate for patients with increasingly complex prior therapy histories?

- How to develop resistance testing as an aid to planning therapy?
- What effect will structured treatment interruptions have?
- How to attack reservoirs of latent HIV infection which are not affected by anti-retroviral therapy eg cellular reservoirs such as resting memory CD4 T cells with integrated proviral DNA or antigen-antibody complexes attached to dendritic cells; and anatomical reservoirs such as the Central Nervous System. This may mean that the virus can never be fully eradicated.

The answers to these questions are outside the scope of this review, and may not be appropriate for this type of methodology. We recognise the difficulties of evaluating therapy in patients with mixed prior drug histories, so the present analysis will focus on patients naïve to antiretroviral therapy and consider the question of initial therapy.

4 Current Service within the West Midlands

Within the West Midlands, the main centres for HIV care are the Heartlands Trust and the University Hospitals Trust (Whittal St GUM clinic). All patients are currently offered triple combination therapy based on the British guidelines[24]. Patients are seen in out-patients approximately every six months (Personal Communication. Drake, S.), although they may request appointments at any other time. The total HIV/AIDS budget in the West Midlands is approximately £5 million for treatment and care, and £4.4 million for HIV prevention (1999/2000 allocation) (Personal Communication. Davies, R.).

A dedicated regional group in the West Midlands has existed for the last four years in order to make decisions regarding the provision of antiretroviral therapy. Over the last four years there has been a gradual escalation in the number and costs of drugs. Until now, requests for increasing combinations of drugs have been accepted according to British guidelines, which have been based on incomplete research such as conference abstracts (Personal communication. Hyde, C., Hawker, J.) In 1998, the group expressed a wish that these decisions should be supported by more substantial evidence, and therefore requested that a systematic review of the evidence of effectiveness be carried out.

5 Previous work

There are many general reviews of the effectiveness of antiretroviral therapy, but few attempt to combine data and quantify the overall effectiveness. Six meta-analyses were found[31-36], and two Cochrane protocols[37; 38]. One study investigated the effectiveness of zidovudine given early in HIV infection or deferred until later, and included seven trials[32]. All of these were in drug-naïve patients. A further meta-analysis[31] analysed the effectiveness of zidovudine *vs* zalcitabine *vs* combination on CD4 count using three trials with mainly naïve patients to produce a model of CD4 count over time. There was one meta-analysis of five trials where the patients were mainly drug-experienced and which used individual patient data[33]. Another meta-analysis used individual patient data and included nine trials of immediate vs deferred zidovudine therapy and six trials of dual therapy with zidovudine and didanosine or zalcitabine. These six trials included a mixture of naïve and experienced

patients and examined mortality and disease progression outcomes[35]. Another study meta-analysed seven trials in order to investigate the difference in response between high and low CD4 subgroups[34], and the remaining study investigated the reductions in disease progression for zidovudine plus lamivudine (vs control treatments), using four trials with a mixture of naïve and experienced patients[36]. The two Cochrane reviews are yet to report. The first will compare reduced drug maintenance regimens with standard triple therapy[37], and the second will compare quality of life outcomes in patients on HAART versus protease inhibitors or other HAART regimens[38].

These published analyses have posed and answered a variety of questions relevant to HIV therapy. Most studies investigated a limited range of drugs, and therefore the aim of the present review is to encompass all the available information and include the full range of licensed drugs.

6 Issues arising from clinical trials

Trials of antiretroviral therapies are complicated by several issues which make it difficult to compare them and difficult to translate effects found in trials to clinical practice:

1. Surrogate outcome measures. Outcome indicators such as CD4 count and plasma viral load are thought to be independent predictors of longer term clinical outcome[39]. Trials frequently measure these surrogate outcomes only, from which it is difficult to estimate the potential clinical effect of therapy.

2. Short duration and early termination. Many trials are of short duration (six months or less). This may not be long enough to estimate the true efficacy of the tested therapy in clinical practice because the full extent of toxicity, resistance, compliance and dropouts has not been evaluated[39]. The demand for new licensed drugs is very high, and therefore the scope for longer trials is small. Larger cohort studies may be more informative. There is also potential for bias if trials are terminated early; for example, patient pressure may result in a trial being stopped due to chance positive results which might not have remained had the trial continued to its designed length.

3. High dropout and crossover rates can introduce bias and confounding.

4. Varying sensitivities and cut-off points of viral load assays. Patients who have viral load values below the cut-off point are assigned the lower level of sensitivity of the assay. Studies which have used the earlier, less sensitive assays may substantially underestimate decreases in viral load. In addition, studies often report the % undetectability, which will vary according to the sensitivity of the assay used[39].

5. History of prior antiretroviral therapy and other baseline characteristics. It is increasingly difficult to recruit patients who have had no prior therapy, and trials may accept different proportions of patients with a variety of previous drug experience. A totally naïve cohort would not reflect clinical practice, but it is also likely that the mix of patients in trials will not reflect clinical practice either because of exclusion criteria. However, the more complicated the baseline drug experience, the more difficult it is to disentangle the results and obtain meaningful estimates of effectiveness.

6. Classification of missing data. Intention-to-treat analyses are the accepted standard for reporting outcomes, but the way in which missing data is classified can affect the results. The missing data can either be excluded from the analysis, or the missing patients can be classified as treatment failures (i.e. viral load returning to detectable concentrations) [39] or their last measurement carried forward. Patients who continue to receive allocated treatments tend to have more favourable outcomes (the survivor effect) so analyses that exclude missing data may overestimate the treatment effects. Conversely, analyses which classify missing data as failure, may be too conservative[39].

7 Question to be addressed & approach taken

The main question to be addressed is: How effective and how cost-effective is antiretroviral therapy in HIV positive patients naïve to prior therapy?

Approach
The effectiveness will be addressed by assessing the improvement in effectiveness with each increase in one drug, and split into the following sub-groups according to the number of drugs: monotherapy *versus* placebo, double therapy *versus* monotherapy, triple *versus* double therapy, quadruple *versus* triple therapy. These sub-groups have been chosen because clinical guidelines and clinical practice have developed in this way. This approach means that all possible combinations of double therapy, for example, are assessed together, and assumed to have similar effectiveness. This notion is clearly reflected in the guidelines and also the demands of clinicians to maintain freedom to prescribe a range of different combinations. As all combinations *may not* be equally effective, a subsidiary analysis of the effectiveness of specific combinations will also be carried out.

We have chosen to review only the randomised controlled trials, as these types of studies are less prone to bias than other designs. However, there are limitations in the trials available (as outlined in the previous section). In particular, the short term nature of the trials does not allow prediction of long term clinical outcome. Additionally, the variation in length of trial, dropout rates, nature of the patients, previous treatment, nature of the drugs (and so on) makes interpretation difficult.
In this review, we have attempted to deal with problems of established resistance to antiretroviral therapy by restricting the patients to those naïve to prior therapy. The other variables are investigated for their effect on the outcome by meta-regression techniques. Although imperfect, they will give some indication of the strength of the effect of these factors. The variable nature of the studies available means that definitive estimates may not be possible.

Summary Box 1: Background

- HIV infection is an important public health problem
- There are approximately 3000 new infections per year in the UK
- As yet there is no cure for HIV but treatment is available to slow progression. This is expensive.
- Multiple combinations of antiretroviral drugs are increasingly used and it is important to examine their effectiveness and cost-effectiveness.
- This review is an attempt to evaluate the effectiveness of different numbers of drug combinations in naïve patients, explore the effectiveness of specific combinations, and evaluate their cost-effectiveness.

8 Methods

8.1 Project group

The project group consisted of Rachel Jordan (main reviewer), Lisa Gold (co-reviewer and economist) and Chris Hyde (Senior Reviewer). The project group met at regular intervals in order to discuss progress, decide direction and resolve any problems.

8.2 Search strategy

- Primary studies were identified by searching the following databases:

MEDLINE	1966-end 1999
EMBASE	1980-end 1999
Cochrane Controlled Trials Register	To end 1999
CINAHL	To end 1999
PSYCHLIT	To end 1999
Social Science Citation Index	To end 1999
ISI Index to Scientific & Technical Proceedings	To end 1999
IBSS	To end 1999
Healthstar	To end 1999
NHS EED	To end 1999
OHE HEED	To end 1999
NHS HTA	To end 1999
AIDSTRIALS	To end 1999

The last search was completed in March, 2000.

No language restrictions were applied. The following MeSH headings and textwords were used as appropriate:

1. Antiretroviral drug generic name, trade names, common abbreviations
2. "HIV" "AIDS" "human immunodeficiency virus"
3. "Randomised" "Randomized" "Random allocation" "Randomized controlled trial"
4. In MEDLINE, the first two sections of the Cochrane algorithm for identifying controlled trials[40] was also used (see appendix 13.3).

- The following conference abstracts were searched:
  ICAAC 1998
  ICAAC 1999
  Conference of Retroviruses and Opportunistic Infections 1998
  Conference of Retroviruses and Opportunistic Infections 1999
- Published and unpublished trials were sought by contacting the relevant pharmaceutical companies
- Citation lists from reviews and primary studies were studied.

8.3 Inclusion and exclusion criteria

8.3.1 Study design

Randomised controlled trials only were included.

8.3.2 Population

Studies were accepted if they included patients with HIV (at any stage), who were naïve to any previous antiretroviral therapy. "Naïve" was classified as patients with less than six months of prior zidovudine therapy, as this is an appropriate time for resistance to develop. For studies where there were a mixture of naïve and experienced patients, studies were accepted if there were less than 30% with prior experience. Studies were rejected if they included patients aged <12 years. There was no restriction on sex or likely method of infection.

8.3.3 Intervention

Studies were included if the intervention was any licensed antiretroviral agent (or combination) compared with any other antiretroviral agent (or combination) or placebo, or no treatment.

8.3.4 Outcomes

Studies were included if they measured any outcome. All outcomes were recorded, but the main outcomes of interest were:

- CD4 count
- Plasma viral load
- Disease progression
- Death
- Health-related quality of life (HRQL)
- Adverse drug events
- Resource use and costs

The most useful outcomes would be disease progression and death, HRQL and resource-use costs; however, many trials would be measuring surrogate outcomes only.
Studies were included if they had a duration of at least 12 weeks, and measured outcomes at at least 12 weeks.

8.4 Quality assessment

Each included study was assessed by two independent reviewers for the following items (adapted from the York CRD handbook[41]):

- Was randomisation allocation by a third party?
- Were the control and treatment groups comparable at entry?
- Was the treatment blind to the clinician?
- Was the treatment blind to the patient?
- Were those assessing outcomes blind to the treatment?
- Were the groups treated identically other than for named interventions?
- Was the analysis intention-to-treat?

Any discrepancies were resolved by discussion.

8.5 Data extraction

Data was extracted independently by two reviewers using a standard data extraction form. Some of the data were presented only in graphical format, so the data were estimated from the graph using a ruler, accurate to the nearest 0.5mm. Any discrepancies were resolved by discussion.

8.6 Methods of analysis - effectiveness

Two analyses were performed:

1. The main analysis addresses the effectiveness of different numbers of drugs, comparing monotherapy *vs* placebo (or no treatment), dual therapy to monotherapy, triple therapy to dual therapy and quadruple therapy to triple therapy.
2. The second analysis explores the effectiveness of specific combinations of therapy within each level (e.g. zidovudine compared with didanosine monotherapy).

The effects of all drugs in each of these combinations were considered together. Four outcomes were considered separately: change in CD4 count, change in viral load, disease progression or death, and adverse events leading to withdrawal from the study.

Individual outcomes were presented in tabular form and entered into a meta-analysis (using Cochrane Review Manager software version 3.1.1, May 1998) in order to combine the results.

Meta-regression was performed in order to explore any heterogeneity.

8.6.1 Methods of meta-analyses

Data were entered into RevMan 3.1.1. For continuous outcomes (CD4 count and viral load), an overall estimate was produced by using the weighted mean difference method based on the inverse variance method of weighting. For outcomes based on event rate (disease progression and drug-related adverse events) the overall odds ratio was calculated using the Peto method[42]. Forest plots of the data were generated with statistical significance set at $p<0.05$.

In each case, initially a fixed effects model was used to estimate the overall pooled effect. The statistical heterogeneity of the results were then assessed using the Chi-squared method[43], which is automatically calculated in RevMan. Methods for detecting heterogeneity have low power to detect a true difference[44], therefore the p value (as calculated from the

Chi-squared statistic) is not used to determine statistical significance. Instead, a more conservative and accepted approach is that if the Chi-squared result is less than the number of degrees of freedom, then there is no important statistical heterogeneity (difference) between the results of the studies[44]. There are other methods for testing heterogeneity, but in general, all methods are limited and underpowered for detecting heterogeneity.

If heterogeneity was revealed using the fixed effects model, then the heterogeneity was explored using both sensitivity/sub-group analysis and meta-regression techniques (see below).

The raw extracted data required a certain amount of manipulation in order to present it in the appropriate format. For RevMan, meta-analysis of continuous data requires input of the standard deviation of the effect. Where SDs were not quoted, they were calculated from standard errors, 95% confidence intervals, interquartile ranges etc (see appendix 13.4).

Where there were several arms within a trial, which would allow more than one comparison per arm, the number of events and the number of participants were weighted accordingly so that each subject was used only once (Personal communication. Deeks, J.). For example:

	Actual values			***Values used for analysis (using ZDV twice)***		
Arm	*n*	*CD4 count Change*	*Disease Progresison*	*n*	*CD4 count Change*	*Disease Progresison*
ZDV	40	50	20/40	20	50	10/20
ZDV+Did	40	100	10/40	40	100	10/40
ZDV+Zalc	40	100	10/40	40	100	10/40

If the events were very few (e.g. 3/20), then the most useful comparison was chosen rather than splitting the data further.

8.6.2 Methods of meta-regression

Any heterogeneity observed was investigated using the method of meta-regression in STATA 5.0 software[45]. A random effects meta-analysis is extended to estimate the extent to which one or more covariates (for example, trial duration) explain heterogeneity in the treatment effects. STATA fits models with two additive components of variance, representing the variance within studies and the variance between studies. Using the restricted maximum likelihood method, the effect of each covariate on the between studies variance (τ^2) and the regression coefficients examined.

The covariates tested were: duration of trial (or timepoint), baseline CD4 count/viral load, dropout rates, drug dose, specific drug/s, CD4/viral load change measure used (mean/median/change/endpoint), sensitivity of the viral load assay used, blinding and concealment of allocation.

Details of syntax, coding and assumptions are given in the results section and the appendices (15.5-15.7).

Given the limited amount of data (a maximum of 21 data points), meta-regression may be underpowered to clearly define factors affecting the outcome. The use of meta-regression in this context is exploratory, trying to explain heterogeneity rather than quantify the relationship between the effects observed and the variables in the analysis.

8.6.3 Methods of analysis – economic evaluations

Methods and results will be described in section 12.

9 Results

9.1 Quantity and quality of included studies

9.1.1 Quantity

The searches revealed in excess of 2000 hits. Of these, some 700 full papers were retrieved. 236 papers referred to potentially useful trials; the remainder were reviews or useful for background information. Of the potentially useful papers, 81 were included; although this referred to 47 different trials (some papers were substudies of larger trials or duplicate publications) (see figure 3).

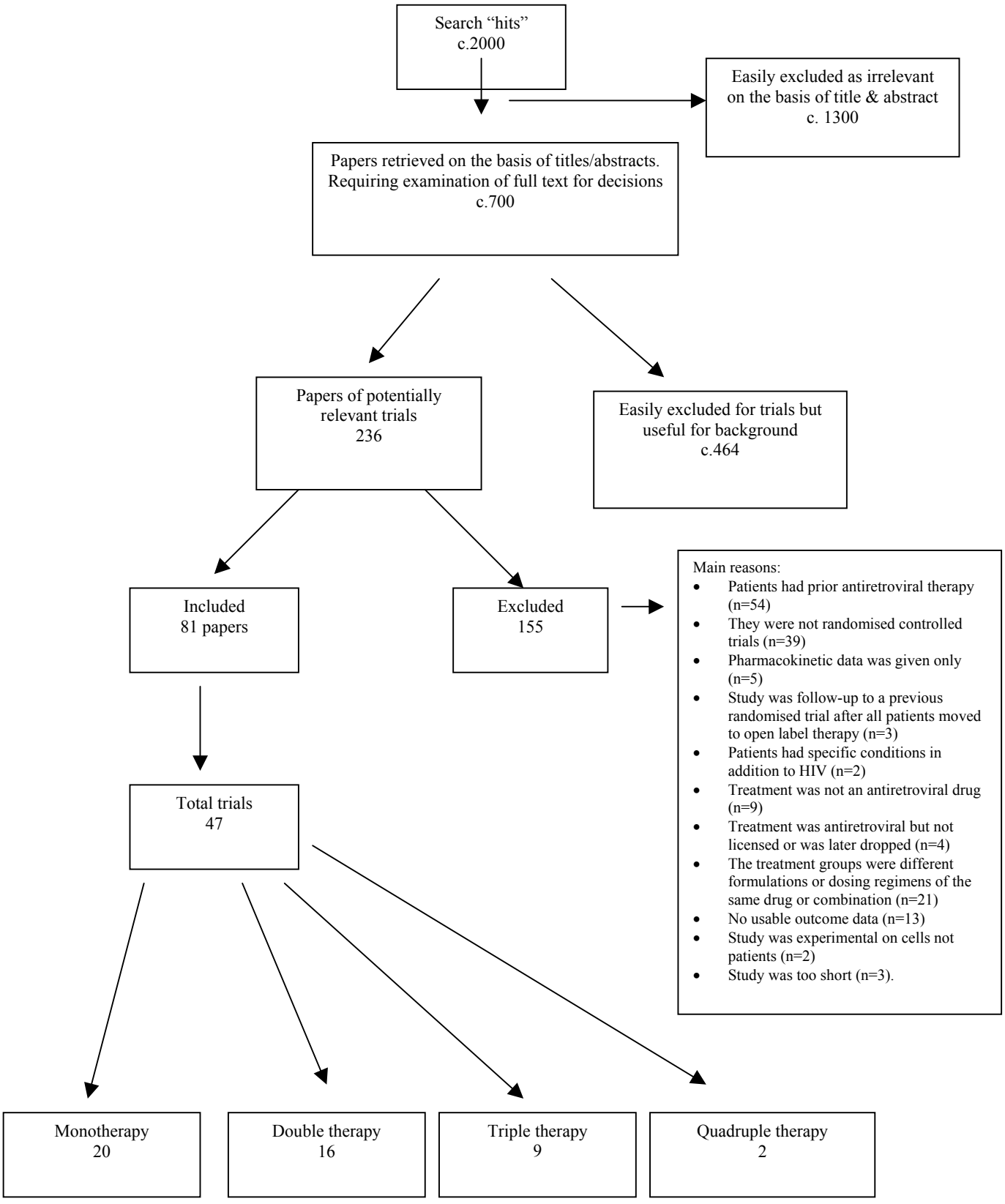
- There were 20 trials where monotherapy versus control monotherapy (or placebo) was tested
- There were 16 trials where double therapy versus double, mono or placebo was tested
- There were 9 trials where triple therapy versus triple, double, mono or placebo was tested
- There were 2 trials where quadruple therapy versus triple, double or placebo was tested

Of the potentially useful papers, 155 were excluded because of the following primary reasons:

- Patients had prior antiretroviral therapy (n=54)
- They were not randomised controlled trials (n=39)
- Pharmacokinetic data was given only (n=5)
- Study was follow-up to a previous randomised trial after all patients moved to open label therapy (n=3)
- Patients had specific conditions in addition to HIV (n=2)
- Treatment was not an antiretroviral drug (n=9)
- Treatment was antiretroviral but not licensed or was later dropped (n=4)
- The treatment groups were different formulations or dosing regimens of the same drug or combination (n=21)
- No usable outcome data (n=13)
- Study was experimental on cells not patients (n=2)
- Study was too short (n=3).

Further information will refer to trials rather than individual papers.

Figure 3 - Flow chart to illustrate search results



Conference Abstracts

33 conference abstracts referred to trials which could be included, which reflects the fact that this is a rapidly developing area. However, limited information was given and therefore the abstracts are not considered further in this review. For completeness, it would have been useful to search the conference abstracts of other key conferences. However, given the general time constraints, and the limited information probably available, these were not sought.

9.1.2 Quality

Table 6 indicates the quality of the included trials. The quality of the papers giving the main (or only) study results is presented only. All the included trials were randomised. Four studies were part of larger trials but are included because the results of the subset of patients naïve to prior antiretroviral therapy are given separately[46-50]. In two trials the patients were stratified or minimised during randomisation by prior therapy[47; 49; 50] and in the remainder, the naïve patients were analysed separately without prior stratification.

Details about the allocation of patients were given in about a third of trials. Where stated, patients were allocated to groups by a third party, usually at a central location.

In general, control and treatment groups within trials appeared comparable at entry for important characteristics such as age, sex, baseline CD4 count and baseline viral load, HIV stage and presence and duration of previous antiretroviral therapy.

In most trials, both patients and clinicians were blind to their assigned treatment. However, there were eight trials where the treatment was open label[46; 51-57]. In one other, only the zidovudine was given open label[58]. In one trial[51] the patients were not blinded because of the complexities of the cyclical treatment arm, but in the remainder of studies there was no reason given for not blinding the patients and clinicians. Trials with non-blinded treatment were accepted and included in the analysis. In one study, the patients were allocated to two groups in an open way, and then blindly randomised to each of three treatments within each group[59]. In order to maintain the highest quality standards, this trial was treated as two separate studies.

Table 6a Quality assessment results – monotherapy combinations

N=No Y=Yes NS=Not stated/unclear

Trial identifier	**Fischl**		**CONCORDE**	**VACS 298**		**Gill**	**Mannucci**	**EACG 016**	**Kinloch-de-Loes**	**EACGS**
Paper ID	Richman, 1987[60]	Fischl, 1987[61]	Anon, 1994[62]	O'Brien, 1996[63]	Hamilton, 1992[64]	Gill, 1991[65]	Mannucci, 1994[66]	Mulder, 1994[67]	Kinloch-de-Loes, 1995[68]	Cooper, 1993[69]
Was randomisation allocation by third party?	NS (Y) See Fischl	Y	Y	NS	NS	NS	NS	NS	NS	NS
Were the control and treatment groups comparable at entry?	NS (Y) See Fischl	Y	Y	Y	Y	NS	Y	Y	Y	Y
Was the treatment blind to the clinician?	Y	Y	Y	NS (Y) See Hamilton	Y	Y	Y	Y	Y	Y
Was the treatment blind to the patient?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were those assessing outcomes blind to the treatment?	NS	NS	Y	NS (Y) See Hamilton	Y	Y	NS	Y	NS	Y
Were the groups treated identically other than for named interventions?	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Was the analysis intention-to treat?	NS (Y) See Fischl	Y	Y	Y	Y	NS	Y	Y	Y	Y

Trial identifier	**DATRI 002**	**Evers**	**Davey**	**Nordic**	**ISS 902**	**ACTG 116A**	**Koot**	**NHF-ACTG 036**	**ACTG 114**	**ACTG 019**
Paper ID	Niu, 1998[70]	Evers, 1998[56]	Davey, 1993[71]	Nielsen, 1996[72]	Floridia, 1997[57]	Dolin, 1995[48]	Koot, 1993[73]	Merigan, 1991[74]	Bozette, 1995[75]	Volberding, 1995[76]
Was randomisation allocation by third party?	Y	NS	NS	NS	Y	NS	NS	NS	NS	NS
Were the control and treatment groups comparable at entry?	Y	Y	NS	NS	Y	Y	Y	Y	Y	Y
Was the treatment blind to the clinician?	Y	N	Y	NS	N	Y	Y	Y	NS	Y
Was the treatment blind to the patient?	Y	N	Y	NS	N	Y	Y	Y	Y	Y
Were those assessing outcomes blind to the treatment?	Y	NS	NS	NS	NS	Y	NS	NS	NS	Y
Were the groups treated identically other than for named interventions?	NS	NS	NS	NS	NS	NS	NS	NS	NS	N Placebo arm offered open label ZDV if CD4 <500.
Was the analysis intention-to treat?	Y	N	Y	NS	Y	Y	NS	Y	NS	Y

Trial identifier **Paper ID**	**ACTG 019** Volberding, 1990[77]	**ACTG 016** Fischl, 1990[78]	**Lane** Lane, 1989[79]
Was randomisation allocation by third party?	Y	NS	NS
Were the control and treatment groups comparable at entry?	Y	Y	Y
Was the treatment blind to the clinician?	Y	Y	Y
Was the treatment blind to the patient?	Y	Y	Y
Were those assessing outcomes blind to the treatment?	Y	NS	NS
Were the groups treated identically other than for named interventions?	NS	NS	NS
Was the analysis intention-to treat?	Y	Y	Y

Table 6b Quality assessment results – double combinations

N=No Y=Yes NS=Not stated/unclear

Trial identifier	**Yarchoan**	**Vella**	**ACTG 175**	**DELTA-1**		**NUCA 3001**	**NUCB 3001**	**Kaulen**	**Protocol 34,225-02**	**Foudraine**	**Izopet**
Paper ID	Yarchoan, 1994[53]	Vella, 1996[80]	Hammer, 1996[47]	Anon, 1999[49]	Anon, 1996[50]	Eron, 1995[81]	Katlama, 1996[82]	Kaulen, 1993[83]	Schooley, 1996[84]	Foudraine, 1998[54]	Izopet, 1999[85]
Was randomisation allocation by third party?	Y	NS	Y	NS (Y) See Anon 1996	Y	NS	Y	NS	NS	NS	NS
Were the control and treatment groups comparable at entry?	Y	Y	Y	Y	Y	Y	N Greater prior therapy in ZDV arm.	Y	N VL lower in ZDV/Did arm. Also more in CDC A.	Y	Y
Was the treatment blind to the clinician?	N	Y	Y	Y	Y	Y	Y	N	Y	N	N
Was the treatment blind to the patient?	N	Y	Y	Y	Y	Y	Y	N	Y	N	N
Were those assessing outcomes blind to the treatment?	NS	NS	NS	NS (Y) See Anon 1996	Y	NS	NS	NS	NS	NS	NS
Were the groups treated identically other than for named interventions?	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Was the analysis intention-to treat?	NS	Y	Y	Y	Y	Y	Y	NS	Y	NS	NS

Trial identifier	**ACTG 306**	**ALBI**	**M50003**	**A1455-053**	**NAT002**
Paper ID	Kuritzkes, 1999[59]	Molina, 1999[55]	Moyle, 1997[86]	Fisher, 1998[87]	Fisher, 1998[87]
Was randomisation allocation by third party?	NS	Y	NS	NS	NS
Were the control and treatment groups comparable at entry?	Y	Y	Y	Y	Y?
Was the treatment blind to the clinician?	Y	N	Y	Y	N
Was the treatment blind to the patient?	Y	N	Y	Y	N
Were those assessing outcomes blind to the treatment?	NS	NS	NS	NS	NS
Were the groups treated identically other than for named interventions?	NS	NS	NS	NS	NS
Was the analysis intention-to treat?	Y	Y	Y	NS	NS

Table 6c Quality assessment results – triple and quadruple combinations

N=No Y=Yes NS=Not stated/unclear

	TRIPLE									*QUADRUPLE*	
Trial identifier	**Floridia**	**ACTG 261**	**INCAS**	**PISCES**	**CHEESE**	**AVANTI-1**	**Study 006**	**EARTH-1**	**PROAB 2002**	**QUATTRO**	**Kirk**
Paper ID	Floridia,1999[88]	Friedland, 1999[89]	Montaner, 1998[90]	Revicki, 1999[58]	Cohen Stuart, 1999[52]	Gatell, 1999[91]	Staszewski, 1999[92]	Garcia, 1999[93]	Haubrich, 1999[94]	Anon, 1999[51]	Kirk, 1999[46]
Was randomisation allocation by third party?	Y	NS	Y	NS	NS	Y	NS	Y	Y	NS	Y
Were the control and treatment groups comparable at entry?	Y	Y	N VL lower in triple arm.	Y	Y	Y	Y	N IDU, %Males differed	N Prior therapy higher in low and medium Amp arms; CD4 lower in medium Amp arm.	Y	N Fewer cases of AIDS in Indinavir arm.
Was the treatment blind to the clinician?	Y	Y	Y	Y Except ZDV	N	Y	N	N	N Except Amp 2100mg and P	N	N
Was the treatment blind to the patient?	Y	Y	Y	Y Except ZDV	N	Y	N	N	N Except Amp 2100mg and P	N	N
Were those assessing outcomes blind to the treatment?	NS	NS	Y?	NS	NS	NS	NS	NS	NS	NS	NS
Were the groups treated identically other than for named interventions?	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Was the analysis intention-to treat?	Dis Prog = Y Primary efficacy analysis = N	Y	Y	Y	Y	Y	Y Except CD4.	Y	NS	Y	Y

Details about the blinding of those assessing outcomes were infrequent, although when mentioned, the blinding did occur. If the clinical outcomes were assessed by the attending clinician, then in these cases most were blinded. Laboratory outcomes might be assumed to be blind although this cannot be determined.

No trials were reported as treating the patients any differently (other than assigned therapy) between allocated groups, but the information was not clearly given in the report. It might be assumed that in the trials where treatment was blinded, the patients would have been treated identically.

An intention-to-treat approach to analysis was taken in the majority of trials, although in many cases, there was a loose interpretation of "intention-to-treat analysis". In several trials, completeness of reporting was an issue – for example, numbers of patients were not clearly given at each timepoint.

Overall the studies were of good quality, and it appears also that over time the reporting of quality issues has improved.

9.2 Study characteristics

The characteristics of the included papers are given in Tables 7(a) – (d) in appendix 15.1 – the volume of information precludes their inclusion within the main body of the text. For drug abbreviations, see front of report.

All papers reported were randomised controlled trials, varying in size from 16[127] to 2124[50]. The majority of subjects were men (usually over 80%), and all were over the age of 12 with an average age (where stated) ranging between 27 and 40. Mean (or median) baseline CD4 count ranged between 83 and 660 cells per μl, and log plasma viral load between 2.35 and 7.35 copies per ml. Clinical stage was infrequently given, but where detailed, more patients were classified as asymptomatic than other stages. Most patients had no prior antiretroviral treatment; a minority had up to six months prior zidovudine; and one trial[86] included up to 20% drug-experienced patients. Two trials[46; 47] reported the results separately for a naïve stratum. Early trials were assumed to include naïve patients if it was not mentioned in the report.

The interventions were all monotherapy, dual therapy, triple therapy or quadruple therapy against placebo (or no treatment) or other antiretroviral drugs and combinations.

The most common monotherapy vs placebo was zidovudine at 500-1500mg per day, and there were also several trials which compared zidovudine with didanosine (400-750mg per day) or zalcitabine (2.25mg per day).

The most common dual therapies were:

- zidovudine + didanosine, (N + N)
- zidovudine + zalcitabine, (N + N)
- zidovudine + lamivudine, (N + N)
- stavudine + didanosine, (N + N)
- zidovudine + saquinavir (N + PI)

The triple therapies studied were:

- zidovudine + didanosine + nevirapine, (N + N + NN)
- zidovudine + didanosine + delavirdine (N + N + NN)
- zidovudine + zalcitabine + saquinavir. (N + N + PI)
- zidovudine + lamivudine + loviride* (N + N + NN)
- zidovudine + lamivudine + indinavir (N + N + PI)
- zidovudine + lamivudine + efavirenz (N + N + NN)
- zidovudine + lamivudine + saquinavir (N + N + PI)
- zidovudine + lamivudine + amprenavir (N + N + PI)
- stavudine + lamivudine + ritonavir (N + N + PI)

The quadruple therapies studied were:

- Zidovudine + lamivudine + loviride* + zalcitabine (N + N + NN + N)
- 2NRTIs + Ritonavir + saquinavir (N + N + 2PI)

*Although loviride is no longer licensed, these trials were included because of the paucity of information available.
N = Nucleoside Reverse Transcriptase Inhibitor
NN = Non- Nucleoside Reverse Transcriptase Inhibitor
PI = Protease Inhibitor

There were also some unusual interventions such as cyclical or alternating therapies and intermittent therapies. The intermittent therapies have not been included in any analyses but are presented in the characteristics tables for completeness, and the alternating therapies have been included as monotherapy or dual therapies as appropriate. Data from trials comparing immediate zidovudine with deferred zidovudine were extracted at the timepoint when patients allocated to the "deferred" arm were still taking placebo. The comparison then became classified as zidovudine *vs* placebo.

The main outcomes measured were CD4 count, plasma viral load, death, disease progression and drug-related adverse events. Other outcomes measured less frequently included quality of life, resistance, weight, adherence, serum neopterin, serum β_2M and serum p24 antigen. More recent combination trials were more likely to measure viral load (a more recently developed indicator) than earlier monotherapy trials. Most studies measured CD4 count, but fewer later studies measured disease progression. This may be because the more recent trials tended to be of shorter duration than earlier trials (range of follow-up 12 weeks to 4.8 years), and that there would be a shorter time to disease progression in early trials with monotherapy. Most trials had a median (or mean) follow-up of between 24 and 64 weeks.

Outcomes such as CD4 count, viral load and death were relatively clearly given. However, disease progression was defined differently between trials. Where there was a choice, the definition which presented the number of patients moving from one category to the next (e.g. from asymptomatic to ARC or Category A to B etc) was used. Adverse events were not always clearly given. Data was only used if it was clear that the event referred to the number of patients who had needed to drop out of the trial because their drug-related adverse event was so severe.

The criteria for patients to stop their assigned treatment was not well reported. Where stated, it was usually based on disease progression, a specified CD4 count or serious adverse event.

In many of these cases, patients could be offered open label alternative therapy (often the new drug(s) being tested)[50; 55; 62; 64; 76; 86; 93].

9.3 Effectiveness results (comparing different levels of therapy)

The effectiveness results are presented separately by outcome. Within each outcome is the description of any assumptions which were needed, the methods used, the results of the meta-analysis, any sensitivity analysis or meta-regression performed. The results are given separately for each level of therapy and an overall conclusion drawn.

9.3.1 CD4 count

CD4 data

Table 8 presents the comparisons derived from the included trials. The data are given by trial and level of therapy, and include treatment, patient numbers, baseline CD4 count, change relative to placebo and timepoint at which CD4 count was measured.

CD4 - Rules and assumptions

1. The primary outcome was change in CD4 count (cells per μl).
2. It was assumed that change in CD4 count would be normally distributed. Where given, mean change was used. If medians were given only, then they were assumed equivalent to means.
3. If measures of variance were only given for the end CD4 count, then this value was used instead of the change in CD4 count.
4. If no measures of variance were given, then the data could not be used for the meta-analysis (as no weighting could be calculated) but the outcome would be presented separately for reference.
5. Usually CD4 count was given at various time intervals. The time interval chosen was the longest point at which at least 50% of the participants in each arm were still included.

Table 8 Change in CD4 count

calculated using: * median †endpoint. ‡ not contributing to combined result

Trial identifier	*Timepoint (weeks)*	*Treatment arm*	*n*	*Baseline CD4 count (cells per μl)*	*Control Arm*	*n*	*Baseline CD4 count (cells per μl)*	*Relative CD4 change (cells per μl)*	*95% CI*
Monotherapy *versus* placebo									
VACS 298[64]	69	ZDV	102	359.7	Placebo	106	348.7	33	-35, 101
ACTG 016[78]	24	ZDV	175	-	Placebo	144	-	52.5*	28, 77
Kinloch-de-Loes[68]	26	ZDV	30	477	Placebo	29	519	137†	-6, 280
Koot[73]	52	ZDV	22	350	Placebo	18	330	17†	-14, 138
DATRI 002[70]	24	ZDV	9	603.8	Placebo	13	619.2	170†	-275, 615
Evers[56]	62	ZDV	47	259	No treatment	51	268	9†	-76, 94
CONCORDE[62]	145	ZDV	482	-	Placebo	468	-	43*	12, 74
NHF-ACTG 036‡[74]	24	ZDV	48	287	Placebo	61	282	49†	-
Lane‡[79]	12	ZDV	9	467	Placebo	9	430	54	-
Fischl‡[61]	16	ZDV	82	120.9	Placebo	74	121	48†	-
Davey‡[71]	12	ZDV	12	588	Placebo	11	588	-11	-
Double therapy *versus* monotherapy									
NUCA 3001[81]	48	ZDV+Lam	24	380	ZDV	28	349	49	-17, 115
	48	ZDV+Lam	27	366	ZDV	28	349	57	-16, 130
	48	ZDV+Lam	27	366	Lam	27	340	6	-58, 70
	48	ZDV+Lam	24	380	Lam	27	340	14	-57, 85
ACTG 175[47]	128	ZDV+Did	67	372	ZDV	68	372	64	10, 117
	128	ZDV+Did	67	372	Did	67	372	-8	-61, 46
	128	ZDV+Zalc	66	372	ZDV	68	372	85	28, 141
	128	ZDV+Zalc	66	372	Did	67	372	13	-43, 70
Kaulen[83]	36	ZDV+Zalc	43	221	ZDV	42	259	64†	-13, 141
M50003[86]	52	ZDV+Zalc	129	-	ZDV	127	-	79*†	44, 114
ACTG 306[59]	24	ZDV+Lam	49	401	Stav	16	424	73	3, 142
	24	Stav+Lam	53	405	Stav	16	424	36	-31, 103
	24	ZDV+Lam	49	386	Did	18	398	22	-33, 77
	24	Did+Lam	52	387	Did	18	398	-3	-57, 52

Trial identifier	*Timepoint* *(weeks)*	*Treatment arm*	*n*	*Baseline CD4 count* *(cells per μl)*	*Control Arm*	*n*	*Baseline CD4 count* *(cells per μl)*	*Relative CD4 change* *(cells per μl)*	*95% CI*
QUATTRO[51]	64	ZDV+Lam	29	180	ZDV-lam-lov-Zalc	30	170	22*	-38, 82
NUCB 3001[82]	24	ZDV+Lam	54	280	ZDV	53	260	90	35, 145
DELTA-1[50]	80	ZDV+Did	435	214	ZDV	212	215	66*	41, 91
	80	ZDV+Zalc	426	213	ZDV	212	215	47*	27, 67
Protocol 34,225-02[84]	48	ZDV+Did	59	147	ZDV	30	146	33†	-27, 93
	48	ZDV+Zalc	61	135	ZDV	30	146	54†	-6, 114
Yarchoan[53]	63	ZDV+Did	16	183	ZDV alt. Did	10	202	-15.0	59
Vella‡[80]	16	ZDV+Saq	9	152	ZDV	9	168	15*	-
	16	ZDV+Saq	10	173	ZDV	9	168	61*	-
	16	ZDV+Saq	10	173	Saq	10	173	58*	-
	16	ZDV+Saq	9	152	Saq	10	173	12*	-
NAT 002‡[87]	20	Stav+Did	14	266.9	Did	3	240.9	37*	-
	20	Stav+Did	14	235	Did	3	240.9	17*	-
	20	Stav+Did	9	262	Did	3	240.9	-82*	-
	20	Stav+Did	10	270.4	Did	3	240.9	-120*	-
Triple therapy *versus* double therapy									
INCAS[90]	52	ZDV+Did+nev	26	387	ZDV+Did	52	390	52	-17, 121
	52	ZDV+Did+nev	26	387	ZDV+Nev	47	346	145	73, 217
ACTG 261[89]	48	ZDV+Did+del	35	294	ZDV+Did	104	284	15	-44, 74
	48	ZDV+Did+del	35	294	ZDV+Del	101	295	70	11, 129
	48	ZDV+Did+del	35	294	Did+Del	108	305	31	-28, 90
Study 006[92]	48	Efa+ZDV+Lam	97	350	Efa+Ind	43	344	21	-41, 83
	48	Ind+ZDV+Lam	80	341	Efa+Ind	43	344	5	-53, 62
EARTH-1[93]	52	Stav+Lam+Rit	10	640	ZDV+Did	29	621	115	28, 202
	52	Stav+Lam+Rit	10	640	ZDV+Zalc	28	597	178	93, 262
	52	Stav+Lam+Rit	10	640	Stav+Did	31	662	115	28, 202
Floridia‡[88]	24	ZDV+Did+nev	25	68	ZDV+Did	25	97.9	39	-
AVANTI-1‡[91]	52	ZDV+Lam+Lov	48	270	ZDV+Lam	39	270	54*	-
PROAB 2002‡[94]	12	ZDV+lam+Amp	15	405	ZDV+Lam	7	422	41*	-
	12	ZDV+lam+Amp	20	312	ZDV+Lam	7	422	-7*	-

Trial identifier	*Timepoint* *(weeks)*	*Treatment arm*	*n*	*Baseline CD4 count* *(cells per μl)*	*Control Arm*	*n*	*Baseline CD4 count* *(cells per μl)*	*Relative CD4 change* *(cells per μl)*	*95% CI*
	12	ZDV+lam+Amp	18	401	ZDV+Lam	7	422	2*	-
Quadruple therapy *versus* triple therapy									
Kirk‡[46]	24	Rit+Saq+2NRTIs	20	165	Ind+2NRTIs	38	91	22*	-
	24	Rit+Saq+2NRTIs	20	165	Rit+2NRTIs	42	111	7*	-

CD4 - Combining the data

Figure 4 presents a Forest Plot of the change in CD4 count; treatment arms relative to control for monotherapy vs placebo (or no treatment), double vs mono, triple vs double and quadruple vs triple. The figure shows the number of patients in each arm, the mean CD4 change (and SD), the weighted mean change of the treatment relative to control with its 95% confidence interval, and the % weight given to each arm. Note that the weights given are the contribution to the *total* summary estimate. For each level of comparison, the figure also shows the results of the Chi-squared test for heterogeneity, number of degrees of freedom, and an overall estimate of effectiveness. In addition, at the bottom of the figure, is an overall summary estimate for the effect of adding one drug over the previous regimen.

CD4 - Monotherapy versus placebo (or no treatment)

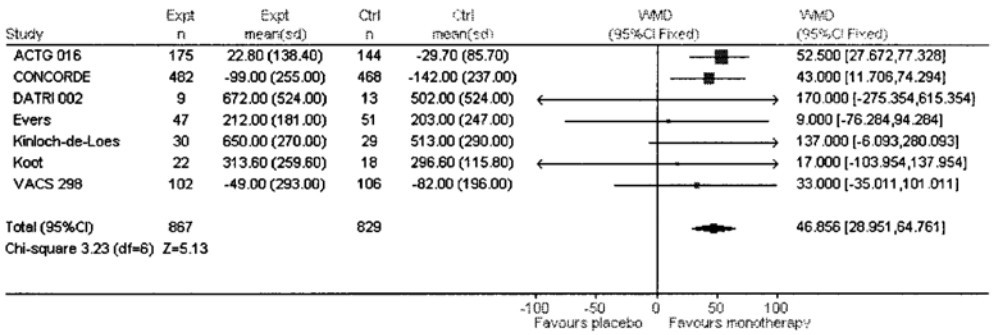
Seven comparisons contributed to this result; a total of 1018 patients taking monotherapy arm and 984 control. All of the monotherapy arms were zidovudine. All comparisons showed point estimates in the positive direction, favouring zidovudine (that is, zidovudine increases CD4 count relative to control). Only the two largest studies showed that treatment was significantly better than control. The chi-square test for heterogeneity was substantially smaller than the degrees of freedom, which suggests that there is no significant heterogeneity between the study results. The overall improvement in CD4 count with monotherapy would therefore be 47 cells per μl (95% CI 29, 65).

CD4 - Double therapy versus monotherapy

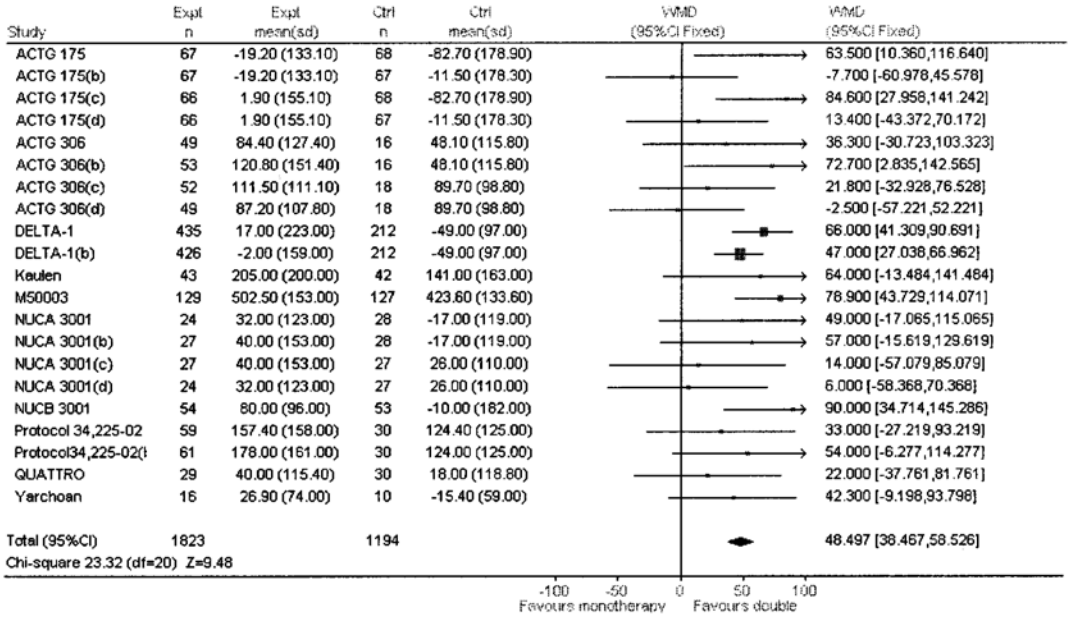
The majority of the 21 comparisons which contributed to the result showed a positive effect for double therapy over monotherapy. Two studies marginally (although not significantly) favoured the monotherapy arm. Only seven of the comparisons individually showed a statistically significant effect. Some significant heterogeneity was observed between the studies, so that the overall result of 49 cells per μl improvement cannot be assumed to be a valid estimate of the summary effect.

Figure 4 Forest Plot to show change in CD4 count by trial, comparison and meta-analysis combined estimate

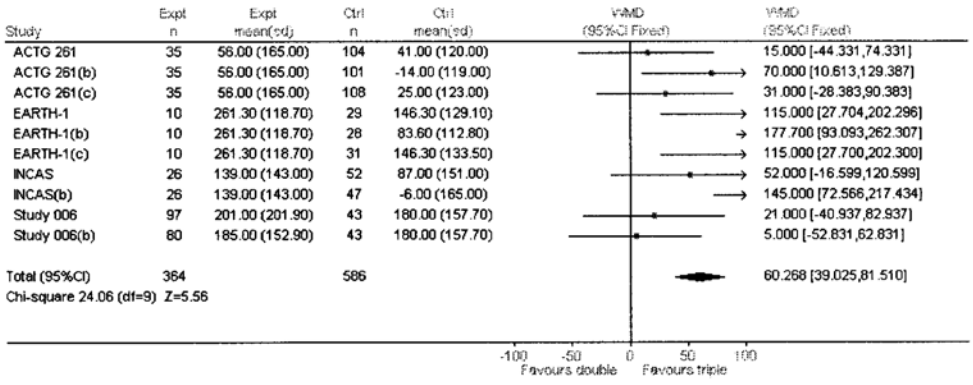
Monotherapy *versus* placebo



Double therapy *versus* monotherapy



Triple therapy *versus* double therapy



Exploring heterogeneity – sensitivity analysis I
It was thought that one of the important possible reasons for heterogeneity could be the actual drugs/combinations which were used. Initially, the more unusual combinations and comparisons (such as lamivudine or saquinavir as comparators, alternating therapies and treatments containing loviride) were removed from the analysis. However, this did not improve the heterogeneity result or alter the effectiveness estimate.

Exploring heterogeneity – meta-regression I
A more complex method was needed to explore heterogeneity. The effects of a range of potential important variables on the CD4 count change were examined firstly individually, using a meta-regression model in STATA. The continuous variables were entered as the data was given, and the categorical variables coded (see appendices 15.6 and 15.7 for codes and definitions). Each of the following variables were tested:

- Continuous:
  - % dropout in the treatment arm
  - % dropout in the control arm
  - timepoint of CD4 measurement (weeks)
  - Baseline CD4 count*
- Categorical
  - Drug dose (control and treatment)
  - Drug name/combination (control and treatment)
  - CD4 change measure used (ie mean/median/change/endpoint)
  - Blinding
  - Randomisation concealment

* Caution should be used when investigating baseline factors which are related to the dependent variable (such as mean CD4 count change). Some statisticians prefer the method not to be used. More complex methods for this do exist, but are outwith the scope of this report.

Appendices 15.5 and 15.6 present the STATA syntax/variables used. However, none of the variables had a material effect on the between studies variance. Therefore, the heterogeneity is not explained by any of the above variables.

CD4 - Triple versus double therapy
10 comparisons contributed to the result. Five showed a significantly positive result for triple therapy over double therapy. The remaining five showed a non-significant positive result. The Chi-squared test revealed significant heterogeneity which needed exploration and meant that the combined effect of 60 cells per µl improvement should be interpreted with caution.

Exploring heterogeneity – meta-regression
None of the included combinations would be considered particularly unusual, so the heterogeneity was explored using meta-regression as above. The same variables were investigated individually, but again, none had a material effect on the between-studies variance. This is likely to reflect the limitation of a small number of trials and the limitations of the technique.

CD4 - Quadruple versus triple therapy

Only one trial (two comparisons) gives information on the effect of quadruple over triple therapy. Unfortunately, there was no information regarding the variances for either comparison. The point estimates both showed an effect favouring the triple arm (22 and 7 cells per μl respectively) although none of the arms showed a significantly different effect on CD4 change (p=0.82).

CD4 - Overall result

It is important to interpret any overall result cautiously. An increase of one drug over the previous regimen encompasses mono vs placebo, double vs mono, triple vs double, and quadruple vs triple. Although only mono vs placebo showed homogeneous results, most of the effects (with the exception of the quadruple comparisons) were in the positive direction and between 47 and 60 cells per μl better than previous regimen.

9.3.2 Viral load

Viral load data

Table 9 presents the comparisons derived from the included trials. The data is given by trial and level of therapy, and includes treatment, patient numbers, baseline plasma viral load, change relative to placebo and timepoint at which viral load was measured.

Table 9 Change in plasma viral load (VL)

Calculated using: * median †endpoint. ‡ not contributing to combined result

Trial Identifier	*Timepoint (weeks)*	*Treatment Arm*	*n*	*Baseline-VL (log copies per ml)*	*Control Arm*	*n*	*Baseline VL (log copies per ml)*	*Relative VL change (log copies per ml)*	*95% CI*
Monotherapy *versus* placebo									
Kinloch-de-Loes[68]	26	ZDV	20	7.59	Placebo	22		-0.100†	-0.638, 0.438
DATRI 002[70]	24	ZDV	8	5.47	Placebo	10		-0.530†	-2.166, 1.106
VACS 298[63]	17	ZDV	102	-	Placebo	86		-0.600	-0.756, -0.444
Double therapy *versus* monotherapy									
NUCA 3001[81]	24	ZDV+Lam	33	4.4	ZDV	31	4.6	-0.740	-1.039, -0.441
	24	ZDV+Lam	30	4.4	ZDV	31	4.6	-0.650	-0.947, -0.353
	24	ZDV+Lam	30	4.4	Lam	30	4.5	-0.480	-0.764, -0.196
	24	ZDV+Lam	33	4.4	Lam	30	4.5	-0.570	-0.856, -0.284
Vella[80]	16	ZDV+Saq	10	-	ZDV	17	-	-0.24*	-0.75, 0.27
	16	ZDV+Saq	10	-	SAQ	19	-	-0.63*	-1.113, -0.147
DELTA-1[49]	16	ZDV+Did	179	4.71	ZDV	125	4.67	-0.94†	-1.109, -0.771
	16	ZDV+Zalc	108	4.74	ZDV	125	4.67	-0.79†	-0.956, -0.624
QUATTRO[51]	64	ZDV+Lam	28	4.8	ZDV-Lam-Lov-Zalc	27	4.8	-0.05	-0.452, 0.352
ACTG 306[59]	24	ZDV+Lam	45	4.15	Stav	16	4	-0.43	-0.812, -0.048
	24	Stav+Lam	51	4.13	Stav	16	4	-0.66	-1.035, -0.285
	24	ZDV+Lam	46	4.01	Did	18	4.08	-0.11	-0.513, 0.293
	24	Did+Lam	46	4.08	Did	18	4.08	-0.11	-0.513, 0.293
NUCB 3001[82]	24	ZDV+Lam	25	5.33	ZDV	23	5.07	-0.90	-1.211, -0.589
	24	ZDV+Lam	14	3.02	ZDV	14	2.79	-0.60	-0.938, -0.262
Protocol 34,225-02[84]	48	ZDV+Did	59	4.82	ZDV	30	5.04	-0.77†	-1.211, -0.589
	48	ZDV+Zalc	61	5.1	ZDV	30	5.04	-0.54†	-0.983, -0.097
NAT 002‡‡[87]	12	Stav+Did	13	4.02	Did	3	4.49	-0.353*	-
	12	Stav+Did	13	4.17	Did	3	4.49	-0.412*	-
	12	Stav+Did	9	4.24	Did	3	4.49	-0.353*	-
	12	Stav+Did	10	4.4	Did	3	4.49	-0.676*	-

Table 9 continued

Triple therapy *versus* double therapy									
INCAS[90]	52	ZDV+Did+Nev	26	4.24	ZDV+Did	51	4.47	-1.15	-1.867, -0.433
	52	ZDV+Did+Nev	26	4.24	ZDV+Nev	46	4.54	-1.98	-2.557, -1.403
ACTG 261[89]	48	ZDV+Did+Del	15	4.47	ZDV+Did	37	4.3	-0.22	-0.732, 0.292
	48	ZDV+Did+Del	15	4.47	ZDV+Del	34	4.64	-0.34	-0.809, 0.129
	48	ZDV+Did+Del	15	4.47	Did+Del	46	4.41	-0.11	-0.579, 0.359
EARTH-1[93]	52	Stav+Lam+Rit	10	4.55	ZDV+Did	29	4.64	-0.530	-0.976, -0.084
	52	Stav+Lam+Rit	10	4.55	ZDV+Zalc	28	4.6	-0.620	-1.096, -0.144
	52	Stav+Lam+Rit	10	4.55	Stav+Did	31	4.48	-0.390	-0.837, 0.057
Floridia‡[88]	24	ZDV+Did+Nev	24	5.6	ZDV+Did	23	5.6	-1.01	-
AVANTI-1‡[91]	52	ZDV+Lam+Lov	44	4.95	ZDV+Lam	37	4.83	-0.05*	-
PROAB 2002‡[94]	12	ZDV+Lam+Amp	18	5.1	ZDV+Lam	7	4.7	-0.3*	-
	12	ZDV+Lam+Amp	20	4.8	ZDV+Lam	7	4.7	-0.5*	-
	12	ZDV+Lam+Amp	17	5	ZDV+Lam	7	4.7	-0.6*	-

Viral load - Rules and assumptions

The rules and assumptions are very similar to those for CD4 count:

1. The primary outcome was change in log plasma viral load (HIV-1 RNA copies per ml).
2. It was assumed that change in log viral load would be normally distributed. Where given, mean change was used. If medians were given only, then they were assumed equivalent to means.
3. If measures of variance were only given for the end viral load, then this value was used instead of the change in viral load.
4. If no measures of variance were given, then the data could not be used for the meta-analysis (as no weighting could be calculated) but the outcome would be presented separately for reference.
5. Usually viral load was given at various time intervals. The time interval chosen was the longest point at which at least 50% of the participants in each arm were still included.

Viral load - Combining the data

Figure 5 shows a Forest Plot of the change in log plasma viral load; treatment relative to control; for each additional increment of one drug (as CD4 count). Again, the weighted mean change with its 95% confidence interval is presented for each comparison, the results of a chi-squared test for heterogeneity, and an overall estimate presented. In contrast to the CD4 count outcome, a lower viral load signifies a more effective therapy.

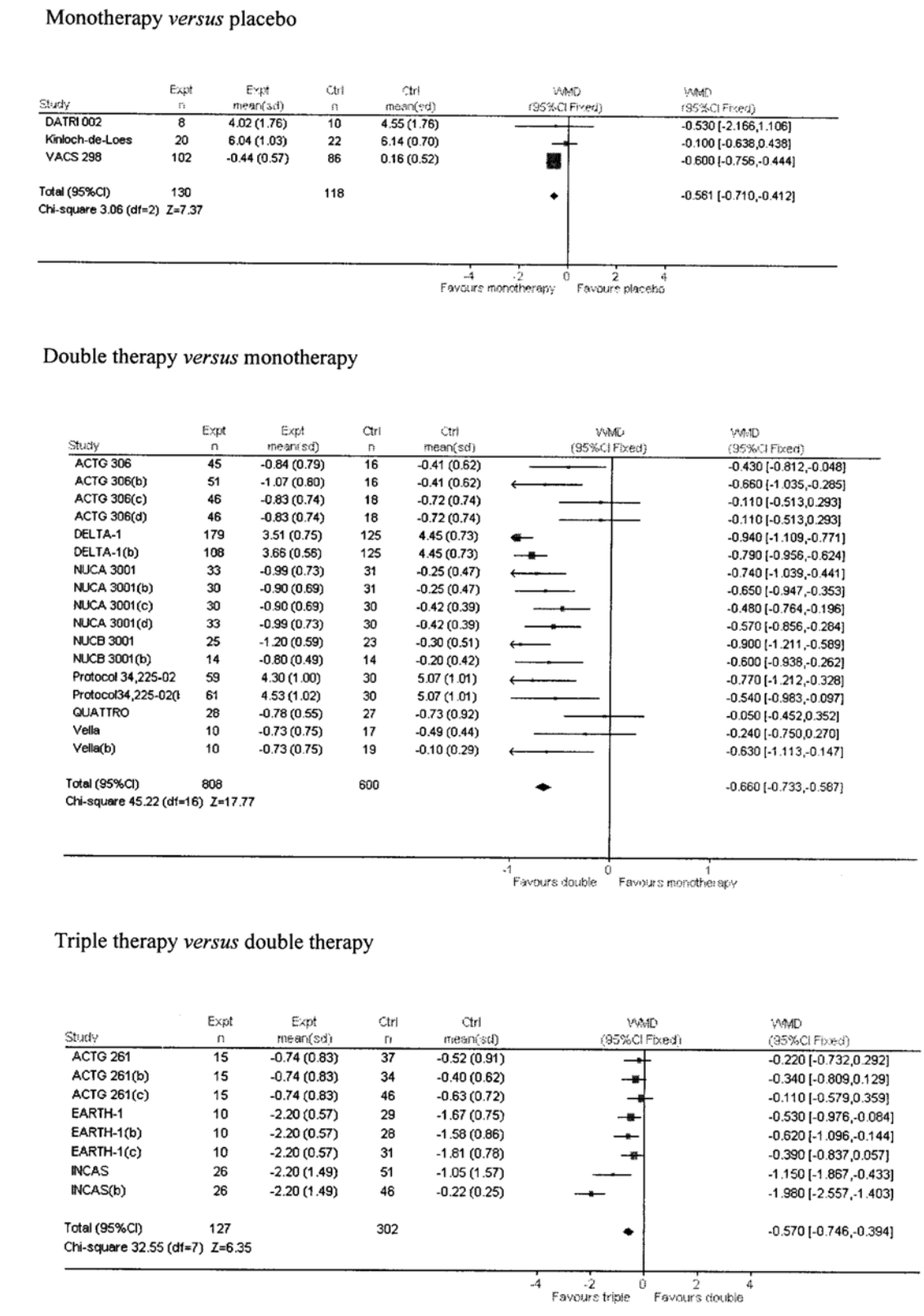
Viral load - Monotherapy versus placebo (or no treatment)

Only three trials contributed to this result – all were zidovudine versus placebo. All showed a result in favour of zidovudine, although only one trial showed a significant result. The chi-squared test indicated that there was heterogeneity present. Since there were only three data points, it was not appropriate to investigate the causes of the differences.

Viral load - Double therapy versus monotherapy

Seventeen comparisons contributed their results. All of these showed a point estimate in favour of the double therapy over the monotherapy, and all but four were significant. However, the chi-squared test indicated substantial heterogeneity which needed to be explored further.

Figure 5 Forest Plot to show change in viral load by trial, comparison and meta-analysis combined estimate



Exploring heterogeneity
Removing comparisons with unusual combinations of drugs did not improve the test for heterogeneity. In a meta-regression the same variables were tested to that of the CD4 outcome, with the addition of a continuous variable to describe the sensitivity of the viral load test (see appendices 15.6 and 15.7). Again, none of the variables had a matreial effect on the between-studies variance.

Viral load - Triple versus double therapy

Eight comparisons contributed to the results. All showed point estimates in favour of the triple therapy, although only four were significant at the 5% level. Significant heterogeneity was present, meaning that the data was not suitable for combination.

Exploring heterogeneity
Meta-regression, with the same independent variables as above, revealed that none of the variables had a matreial effect on the between-studies variance. Again, this is likely to reflect the limitations of both the data and the technique.

Viral load - Quadruple therapy versus triple therapy

There were no data with this comparison.

Viral load - Overall result

There was a large degree of heterogeneity between study effects in each of the three levels of combinations. Despite that, the point estimates consistently favoured the larger number of drugs, and, with extreme caution in the interpretation, it could be suggested that the benefits of an increase of one drug lie in the range 0.56 log to 0.66log lower plasma viral load.

9.3.3 Disease progression or death

Table 10 presents the comparisons from the included trials showing the number of patients who progressed in their HIV status or died over the length of the trial. Although the definitions of disease progression varied (and were sometimes given in several alternative formats), the definitions were consistent within each trial. Where there was a choice, a judgement was required as to the most suitable definition. An attempt was made to capture

Table 10 Results of disease progression/death ‡ not contributing to combined result

Trial identifier	*Duration of trial (weeks)*	*Treatment arm*	*Patients progessing (n)*	*Patients entered (N)*	*Control arm*	*Patients progessing (n)*	*Patients entered (N)*	*Disease progression/death definition*
Monotherapy versus placebo								
VACS 298[64]	119	ZDV	38	170	Placebo	48	168	AIDS
ACTG 106[78]	38	ZDV	15	360	Placebo	36	351	ARC/AIDS/death
ACTG 019[77]	55	ZDV	19	457	Placebo	19	214	Advanced ARC/AIDS detah
	55	ZDV	17	453	Placebo	19	214	
	83	ZDV	7	541	Placebo	8	274	
	83	ZDV	15	549	Placebo	8	274	
Kinloch-de-Loes[68]	26	ZDV	0	39	Placebo	4	38	OIs (CDC stage IV-2)/death
NHF-ACTG 036[74]	41	ZDV	4	92	Placebo	6	101	Advanced ARC/AIDS/death
Koot[73]	104	ZDV	6	29	Placebo	7	23	Not clear. ?AIDS
EACGS[69]	93	ZDV	11	495	Placebo	22	489	CDC stage IV
Evers[56]	52	ZDV	4	47	No treatment	7	51	New OI or lymphoma/death
Fischl[61]	24	ZDV	24	145	Placebo	45	137	1st OI/death
EACG 017[67]	60	ZDV	24	167	Placebo	33	162	CDC stage IV/death
Mannucci[66]	90	ZDV	13	69	Placebo	12	71	Severe ARC/CDC stage IV/AIDS
CONCORDE[62]	152	ZDV	267	877	Placebo	284	872	ARC/AIDS/death
Davey‡[71]	12	ZDV	0	16	Placebo	0	17	AIDS
Double therapy versus monotherapy								
NUCA 3001[81]	52	ZDV+Lam	0	92	ZDV	3	93	AIDS/death
ACTG 175[47]	135	ZDV+Zalc	10	132	ZDV	16	135	AIDS/death
	135	ZDV+Zalc	10	132	Did	12	134	
	135	ZDV+Did	8	134	ZDV	16	135	
	135	ZDV+Did	8	134	Did	12	134	
Vella[80]	16	ZDV+Saq	1	20	ZDV	1	17	AIDS
M50003[86]	90	ZDV+Zalc	5	129	ZDV	5	127	AIDS
QUATTRO[51]	64	ZDV+Lam	5	32	ZDV-Lam-Lov-Zalc	7	34	AIDS/death

Trial identifier	*Duration of trial (weeks)*	*Treatment arm*	*Patients progessing (n)*	*Patients entered (N)*	*Control arm*	*Patients progessing (n)*	*Patients entered (N)*	*Disease progression/death definition*
NUCB 3001[82]	24	ZDV+Lam	1	65	ZDV	0	64	AIDS
DELTA-1[50]	144	ZDV+Did	188	718	ZDV	135	350	AIDS/death
	144	ZDV+Zalc	231	706	ZDV	135	350	
Protocol 34,225-02[84]	72	ZDV+Did	3	59	ZDV	8	30	AIDS/death
	72	ZDV+Zalc	9	61	ZDV	8	30	
Yarchoan[53]	60	ZDV+Did	3	21	ZDV alt. Did	6	20	OI or tumours/death
Triple therapy versus double therapy								
Floridia[88]	48	ZDV+Did+Nev	7	32	ZDV+Did	6	36	AIDS/death
INCAS[90]	52	ZDV+Did+Nev	3	26	ZDV+Did	13	53	CDC B/AIDS/death
	52	ZDV+Did+Nev	3	26	ZDV+Nev	11	47	
AVANTI-1[91]	52	ZDV+Lam+Lov	2	54	ZDV+Lam	2	52	AIDS/death
Study 006[92]	48	ZDV+Lam+Ind	9	148	Efa+Ind	2	74	AIDS/death
	48	ZDV+Lam+Efa	7	154	Efa+Ind	2	74	
EARTH-1[93]	52	Stav+Lam+Rit	1	33	ZDV+Zalc	1	29	AIDS/death

the definition which most adequately explained transition from one accepted HIV category to the next.

Disease progression/death - Combining the data

Figure 6 is a Forest Plot of the individual included comparisons, given by therapy level. The odds ratio of progression or death for treatment over control is given (with 95% CI) for each comparison, and the overall result combined by the Peto Method.

Disease progression/death - Monotherapy versus placebo (or no treatment)

Fifteen comparisons contributed their results. Again, all were zidovudine versus placebo. All but one point estimate favoured the zidovudine monotherapy arm, although only five showed a significant effect at the 5% level. There was significant heterogeneity between the study results, as shown by the chi-squared test.

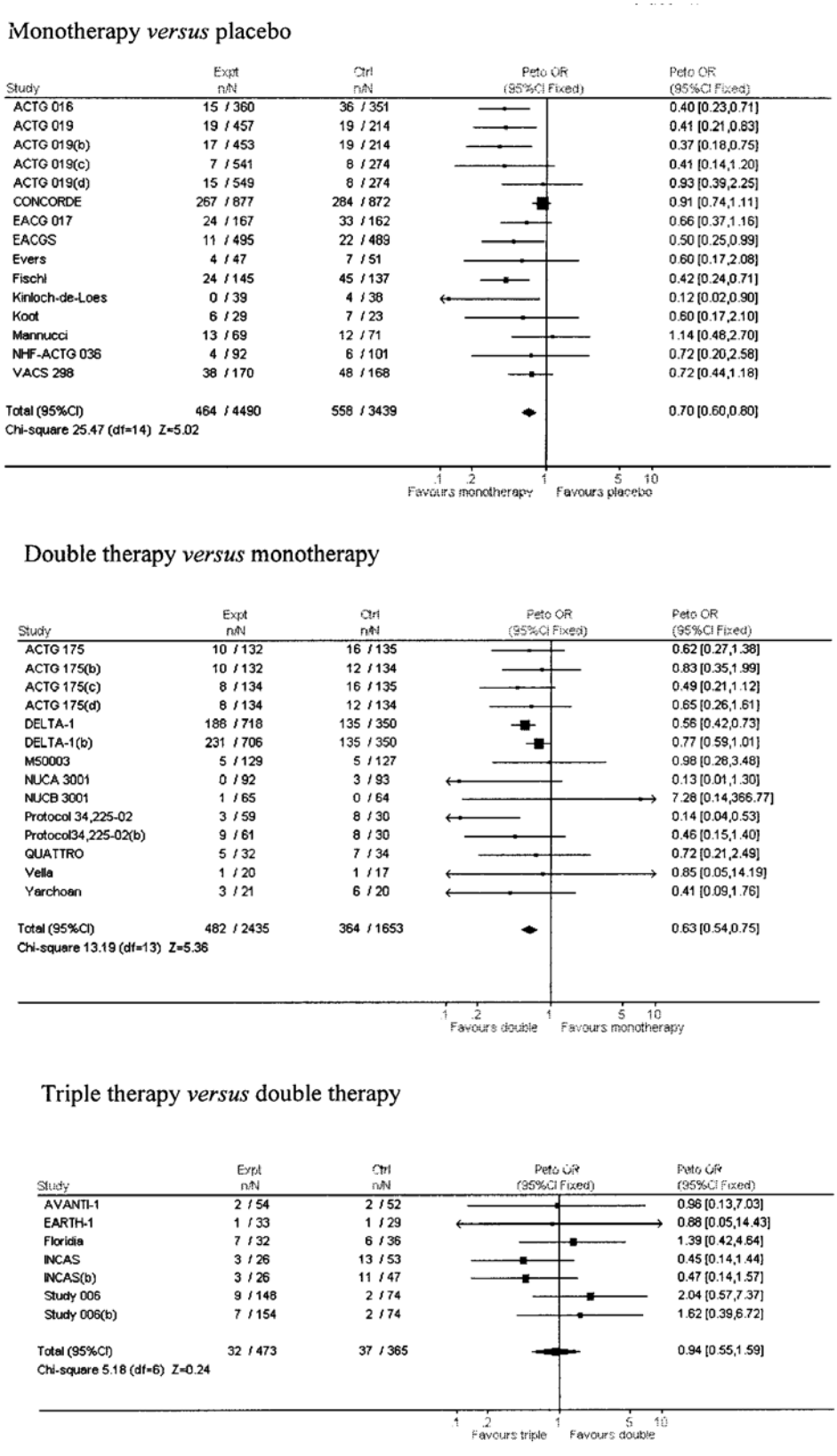
Exploring heterogeneity – meta-regression I

The effects of a range of variables on disease progression or death were examined individually:

- Continuous:
  - % dropout in the treatment arm
  - % dropout in the control arm
  - duration of trial (weeks)
  - Baseline CD4 count
- Categorical
  - Drug dose (control and treatment)
  - CD4 change measure used
  - Blinding
  - Randomisation concealment

It was not necessary to examine drug name, as all of the monotherapy arms were zidovudine only.

Figure 6 Forest Plot to disease progression/death by trial, comparison and meta-analysis combined estimate



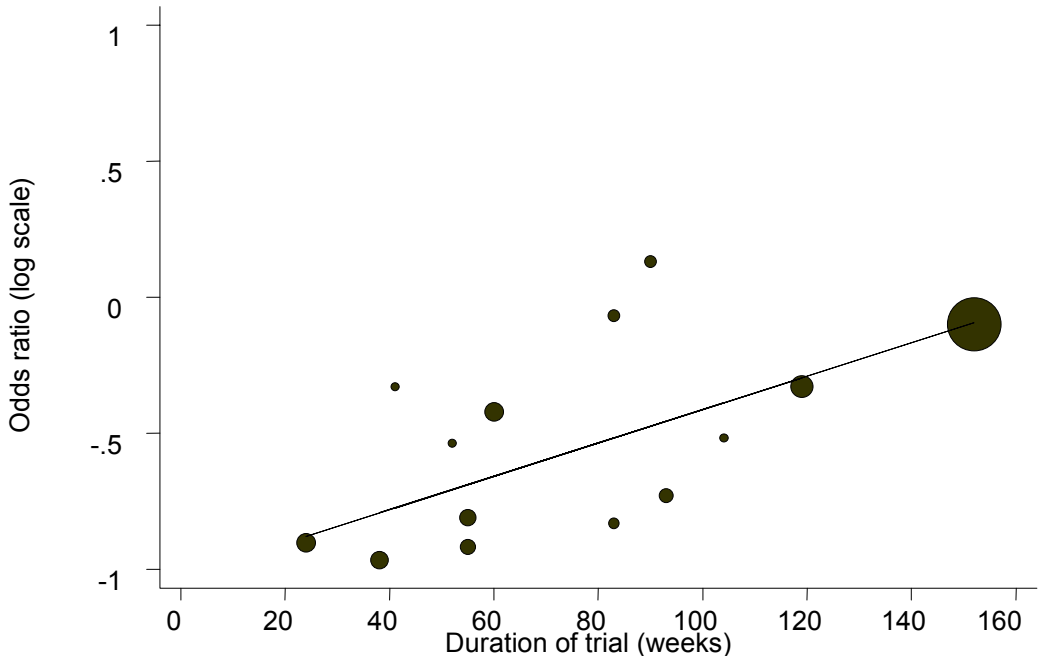
The duration of the trial had a significant effect on the between-studies vaiance, with a coefficient significant at the 5% level (p<0.001), indicating that the log odds ratio increased linearly with increased length of the trial:

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
duration	.00614	.0015459	3.972	0.000	.00311	.0091699
_cons	-1.025919	.1854154	-5.533	0.000	-1.389326	-.6625112

Figure 7 shows the relationship between duration (weeks) and log OR. The equation for the relationship is:

Log OR [disease progression or death] = -1.026 + 0.00614 * [duration of trial (weeks)]

Figure 7 Relationship between Odds Ratio for disease progression/death and trial duration (monotherapy versus placebo)



The results of the meta-regression are given in appendix 15.7.

Disease progression/death - Double therapy versus monotherapy

Fourteen studies contributed to the results. All but one individually favoured double therapy (although only two studies were significant at the 5% level). The chi-squared test indicated that there was a small amount of heterogeneity. Meta-regression models showed that the only variable producing a substantial reduction in an already small between-studies variance (τ^2=0.005 reduced to τ^2=0.000) was the type of drug combination. The coefficient for the combinations ZDV + lamivudine and ZDV + saquinavir were non-significant [0.29 (95% CI -1.0, 1.6) and 0.45 (95% CI -2.4, 3.3) respectively], however the coefficient for the combination of zidovudine + zalcitabine was of borderline significance, p=0.05 [0.34 (95%

CI 0.0005, 0.68)]. The log OR was higher with ZDV+Zalc (ie this combination was less effective) than others. The analysis also showed that the lower drug dose reduced the log OR, that is, it was more effective. However, this does not seem plausible; given the number of comparisons, this could have occurred by chance. Using the combined result with caution, the estimate suggests that the odds ratio might be in the region of 0.6, where double therapy is more effective than monotherapy in reducing disease progression or death.

Disease progression/death - Triple therapy versus double therapy

Seven comparisons contributed to this result. Four of the point estimates favoured triple therapy, and three favoured double therapy, but none of the odds ratios were individually significant at the 5% level. The test for heterogeneity between the studies was not significant, and combined together the results demonstrate that there is no significant difference in disease progression or death between triple therapy and double therapy. However, these results should be interpreted with caution, as they may not have been of long enough duration (or powered) to detect a difference. The lower limit of the 95% CI is 0.55; a very clinically relevant effect.

Disease progression/death - Quadruple therapy versus triple therapy

No data were available.

Disease progression/death – Overall results

Again, it is important to interpret the results with caution. Despite the heterogeneity observed in the zidovudine-placebo comparison, the result favoured the zidovudine arm with a magnitude similar to the double therapy-monotherapy comparison (i.e. an odds ratio of 0.6-0.7). The triple versus double comparison (with few events) limits the conclusions which can be drawn from the data.

9.3.4 Adverse effects

Table 11 presents the comparisons derived from the included trials with data regarding drug-related adverse events. The data shows only the number of patients with an adverse event so severe that it necessitated their withdrawal from the trial. The results are presented by trial and level of therapy, with information on the treatment, numbers of patients dropping out with an adverse event, number of patients starting therapy, and the duration of the trial.

Adverse events - Combining the data

Figure 8 presents a Forest Plot of the drug-related adverse events at each level of therapy. The plot shows the number of adverse events and the total number of patients, and the Peto Odds Ratio of treatment arm relative to control.

Adverse events - Monotherapy versus placebo (or no treatment)

Twelve comparisons contributed to the result. All showed a point estimate in favour of the control arm. Individually, seven trials showed a significant effect (at the 5% level). Overall, the Chi-squared test indicated that there was no significant heterogeneity, and that the combined estimate favoured control with an odds ratio of 2.67 (95% CI 2.10, 3.39). Patients

were significantly more likely to drop out of the trial with a drug-related adverse event if they were in the monotherapy arm rather than the placebo arm.

Adverse events - Double therapy versus monotherapy

Ten comparisons contributed to this result. Again, there was no significant heterogeneity, and the combined estimate produced an odds ratio of 1.02 (95% CI 0.84, 1.24) indicating that there was no difference in dropout rates for drug-related adverse events between double therapy and monotherapy.

Table 11 Results of drug-related adverse events ‡ not contributing to combined result

Trial identifier	*Duration of trial (weeks)*	*Treatment arm*	*Patients dropping out due to adverse events (n)*	*Patients entered (N)*	*Control arm*	*Patients dropping out due to adverse events (n)*	*Patients entered (N)*
Monotherapy versus placebo							
VACS 298[64]	119	ZDV	11	170	Placebo	2	168
ACTG 016[78]	38	ZDV	11	360	Placebo	3	351
ACTG 019[76]	83	ZDV	30	541	Placebo	6	274
	83	ZDV	18	549	Placebo	6	274
Kinloch-de-Loes[68]	26	ZDV	2	39	Placebo	0	38
NHF-ACTG 036[74]	41	ZDV	5	92	Placebo	2	101
EACGS[69]	93	ZDV	27	495	Placebo	10	489
Evers[56]	52	ZDV	6	47	No treatment	0	51
Fischl[60]	24	ZDV	1	145	Placebo	0	137
EACG 017[67]	60	ZDV	4	167	Placebo	1	162
Mannucci[66]	90	ZDV	2	69	Placebo	1	71
CONCORDE[62]	152	ZDV	99	877	Placebo	38	872
Gill‡[65]	12	ZDV	0	11	Placebo	0	6
	12	ZDV	0	11	Placebo	0	6
Lane‡[79]	12	ZDV	0	9	Placebo	0	9
Double therapy versus monotherapy							
NUCA 3001[81]	52	ZDV+Lam	4	46	ZDV	6	47
	52	ZDV+Lam	4	47	ZDV	6	47
	52	ZDV+Lam	4	46	Lam	4	44
	52	ZDV+Lam	4	47	Lam	4	44
NUCB 3001[82]	24	ZDV+Lam	5	65	ZDV	2	64
NAT002[87]	24	Stav+Did	1	16	Did	2	15
DELTA-1[50]	144	ZDV+Did	173	718	ZDV	79	350
	144	ZDV+Zalc	155	706	ZDV	79	350

Trial identifier	*Duration of trial (weeks)*	*Treatment arm*	*Patients dropping out due to adverse events (n)*	*Patients entered (N)*	*Control arm*	*Patients dropping out due to adverse events (n)*	*Patients entered (N)*
Protocol 34,225-02[84]	72	ZDV+Did	5	59	ZDV	3	30
	72	ZDV+Zalc	10	61	ZDV	3	30
QUATTRO‡[51]	64	ZDV+Lam	0	32	ZDV-Lam-Lov-Zalc	0	34
Triple therapy versus double therapy							
Floridia[88]	48	ZDV+Did+Nev	4	32	ZDV+Did	5	36
INCAS[90]	52	ZDV+Did+Nev	4	26	ZDV+Did	7	53
	52	ZDV+Did+Nev	4	26	ZDV+Nev	12	47
AVANTI-1[91]	52	ZDV+Lam+Lov	5	54	ZDV+Lam	6	52
Study 006[92]	48	ZDV+Lam+Ind	30	148	Efa+Ind	5	74
	48	ZDV+Lam+Efa	10	154	Efa+Ind	5	74
EARTH-1[93]	52	Stav+Lam+Rit	4	11	ZDV+Zalc	3	29
	52	Stav+Lam+Rit	4	11	ZDV+Did	7	32
	52	Stav+Lam+Rit	4	11	Stav+Did	2	33
PROAB 2002[94]	12	ZDV+Lam+Amp	5	21	ZDV+Lam	1	20

Figure 8 Forest Plot to show dropout due to drug-related adverse events by trial, comparison and meta-analysis combined estimate

Adverse events - Triple therapy versus double therapy

Ten comparisons contributed to this result. Four comparisons favoured the triple therapy, and six favoured the double therapy; only two of the results were significant at the 5% level. There was significant heterogeneity between the results, but this was not further explored.

Adverse events - Quadruple therapy versus triple therapy

There were no data available for this comparison.

Adverse events – Overall results

The measure used here (dropout rates due to adverse events) was chosen as an indicator of severe adverse events. It is accepted that randomised controlled trials may not be the best method for exploring adverse events. In addition, it is not known how the measure might relate to clinical practice as patients might be under pressure to remain in a short-term trial.

The data shows that there is a significantly increased risk of severe drug-related adverse events with monotherapy compared to control, but no difference between double therapy and monotherapy. It is difficult to tell what effect triple therapy has over double therapy.

9.3.5 Health-related quality of life (HRQL)

Table 12 displays the data available from the included trials regarding quality of life. Six studies included HRQL as an outcome,[58; 86; 91 75; 98; 103] although one did not report any data[91] . Of the five with data, two compared zidovudine with placebo[98; 103], one compared zidovudine with zalcitabine[75], one compared zidovudine + zalcitabine with zidovudine[86] and one compared triple therapy (zidovudine+zalcitabine+saquinavir) with double therapy[58]. Four of the studies used the Medical Outcomes Study Health Ratings as a basis of the quality of life measure and one used the Quality of Well-being scale.

Table 12 Health-related Quality of Life

Trial	*Paper*	*Intervention (n)*	*Quality of life measure*	*Properties and description of scale*	*Baseline Mean*	*Endpoint*	*p*	*Trial duration*
ACTG 016 Substudy	Wu[103]	1.P 2.ZDV (n=70)	MOS-HIV 30 item	30-item version of the Medical Outcomes Study Health Ratings. Self-administered. Various dimensions of functional status and well-being including: physical function, role function, social function, cognitive function, pain, energy, mental health, health distress, patients' own assessment of quality of life and overall health. 0=lowest; 100=highest possible score.	**Overall health at baseline:** 1.P 61.8 2.ZDV 73.6	**Mean change in:** P (n=25) ZDV (n=27) Physical function +2.8 -0.6 Role function -4.2 +1.8 Social function +1.6 0.0 Cognitive function -4.8 +3.1 Overall health +5.0* -6.5 Energy +10.2† -0.9 Pain +3.2 -8.9 Mental health +9.0 +7.1 Health distress +12.8 +5.7 Quality of life +12.0 +0.9	T test changes for placebo vs ZDV *p <0.05 † p <0.01	Week 24
Fischl Substudy	Wu[98]	1.ZDV 2.P (n=32)	1.Quality of Well-being scale (QWB)	Interviewer administered (blinded). Measure of overall health. Three dimensions: mobility, physical & social activity. 0=death; 1=asymptomatic optimal functioning.	1.ZDV (n=16) 0.6486 2.P (n=15) 0.6340	**Mean (SE)** 1.ZDV (n=15) 0.699 (0.039) 2.P (n=9) 0.563 (0.107)	Change from baseline (paired t test) = NS for either group.	Mean blinded study =19 weeks (range 12-24 weeks)
ACTG 114 Substudy	Bozette[75]	1.Zalc 2.ZDV (n=338)	MOS (HIV-PARSE)	Self-report questionnaire. Assesses global health status and functioning (modified from MOS scales), disability, work and symptom impact. Scale from 0 (worst) to 100 (best).	All scores given separately (see paper). **Mean Quality of Life** Zalc (n=174) 52 ZDV (n=164) 49 **Mean Perceived Health Index** Zalc 66 ZDV 66	The differences in symptom impact, disability and work over 48 weeks consistently favoured the ZDV group, and was significant (p<0.05) in all aspects. The differences in health status scores over 72 weeks favoured ZDV (p=0.03 to <0.001). (Significance at 48 weeks not given).		Median follow-up ZDV=54 weeks, Zalc=48 weeks.
M5003 Substudy	Moyle[86]	1.ZDV 2.ZDV + Zalc (n=256)	MOS-HIV 30 item	See before	No details	HRQL was similar between treatment groups throughout. No difference from baseline at 52 or 104 weeks in any dimension. Mean standardised dimensions = 70-80 throughout.	-	Median follow-up 91 weeks
AVANTI-1	Gatell[91]	1.ZDV+Lam+ Lov 2.ZDV + Lam	EQ-5D	5 domains 3 levels	No details	No data reported	-	83% completed 52 weks

Trial	*Paper*	*Intervention (n)*	*Quality of life measure*	*Properties and description of scale*	*Baseline Mean*	*Endpoint*	*p*	*Trial duration*
		(n=106)						
PISCES	Revicki[58]	1.Zalc/ZDV 2.Saq/ZDV 3.Saq/ZDV/zalc (N=993)	1. MOS-HIV Mental Health Summary (MHS) Physical Health Summary (PHS) 2. Visual Analogue Scale (VAS)	**MOS-HIV** A multidimensional construct that includes physical, psychological and social functioning. 10 subscales; responses to questions summed and scored and converted to a 0 to 100 scale (100 indicates better functioning). MHS and PHS scores are based on these 10 subscales. **VAS** 0 = worst imaginable state; 100 = best imaginable health state.	1.Zalc/ZDV* MHS 50.7 (n=309) PHS 52.7 2.Saq/ZDV MHS 49.7 (n=306) PHS 52.7 3.Saq/ZDV/zalc* MHS 49.3 (n=332) PHS 52.3 1. Zalc/ZDV* 79.8 2. Saq/ZDV 77.7 3. Saq/ZDV/zalc* 78.6	**Mean change (SD)(n)** 0.1 (9.7) -2.5 (9.5) (n=249) 0.3 (8.7) -2.2 (9.3) (n=257) 1.4 (9.1) -0.4 (9.1) (n=280) -2.3 (15.4) -2.6 (17.9) 1.0 (17.1)	*Triple vs zalc/ZDV MHS p=0.146 PHS p=0.008 * p=0.002	48 weeks (24 weeks also given)

Triple therapy resulted in a significantly better Physical Health Summary (MOS-HIV) compared with zalcitabine+zidovudine[58] at 48 weeks.

For zidovudine versus placebo, the ACTG 016 study[103] showed significantly better overall health (patient-assessed) and energy scores after 24 weeks for patients in the placebo group compared with the zidovudine group (with the placebo group showing an increase from baseline and the zidovudine a decrease). However, none of the other eight domains showed significantly different scores. Conversely, with the QWB scale[98], by the end of the study, the zidovudine group showed a trend towards higher scores and the placebo group to worse scores, although the change from baseline in each group was not significantly different and there was no test of significance between the groups.

The limited data available make it very difficult to assess the impact of antiretroviral therapy on quality of life, although the ACTG 016 study does support the adverse events data in that patients felt more healthy on placebo than zidovudine.

9.3.6 Resource use and costs

None of the included studies attempted an economic evaluation. Data on healthcare resource was collected by one study[128], which showed that over 48 weeks, although the number of hospital days and office visits were similar between the zidovudine and the zalcitabine groups, patients on zalcitabine had a significntly higher rate of hospital admissions, telephone consultations, regular medications and probability of invasive procedures.

Summary Box 2: General Results

- 81 papers were included, which referred to 47 different randomised controlled trials
- The quality of the studies was generally good – all were randomised and most were double-blind. Allocation concealment was dealt with poorly in 2/3rds of trials, but this is better than in many reviews of trials.
- Six outcomes were assessed: CD4 count, viral load, disease progression, adverse events, health-related quality of life, resource use/costs
- Outcomes were examined at four levels of comparison
    - Monotherapy versus placebo
    - Double therapy versus monotherapy
    - Triple therapy versus double therapy
    - Quadruple therapy versus triple therapy

Summary Box 3: Detailed Results

CD4 count

- Most of the individual studies showed effects favouring the additional drug
- Overall results at each level showed unexplained heterogeneity (except mono vs placebo)
- The combined improved effects of an additional drug at each level probably lie in the range of 45-60 cells per μl

Viral load

- All trials showed effects favouring the additional drug
- Heterogeneity within each level could not be adequately explained
- The combined estimate probably varied between 0.56 log and 0.66 log reduction in viral load

Disease progression/death

- All mono and double comparisons (bar one) favoured the additional drug (OR approx. 0.6 – 0.7)
- Both showed heterogeneity; with the monotherapy this could partly be explained by the length of the trial
- Triple therapy versus double therapy showed no difference in effect

Adverse events

- Monotherapy causes more patients to drop out as a result of drug – related adverse effects than placebo
- Double therapy shows a similar adverse event severity to monotherapy
- With the triple therapy comparisons, the adverse event outcome was difficult to interpret, but was significantly worse with triple therapy in 2/10 trials.

Health-related quality of life and resource use

- Data for both outcomes were very sparse and preclude conclusions

Table 13 Summary of effectiveness results

Comparison	*Mean CD4 count change (95% CI) (cells per μl)*	*Mean plasma viral load change (95% CI) (log copies per ml)*	*Disease progression/death (Odds Ratio) (95% CI)*	*Adverse events (Odds Ratio) (95% CI)*
Monotherapy vs placebo	+ **47** (29, 65)	**-0.56** (-0.71, -0.41)	**0.7** (0.6, 0.8)	**2.62** (2.06, 3.34)
Double therapy vs monotherapy	+ **49** (38,59)	**-0.66** (-0.73, -0.59)	**0.63** (0.54, 0.75)	**1.02** (0.84, 1.24)
Triple therapy vs double therapy	+ **60** (39, 82)	**-0.57** (-0.75, -0.39)	**0.94** (0.55, 1.59)	**1.65** (1.10, 2.45)
Quadruple therapy vs triple therapy	-	-	-	-

Shaded cells – result shows significant (and unexplained) heterogeneity

9.4 Effectiveness of specific drug combinations

9.4.1 Monotherapy

Table 14 and figure 9 display the results of the monotherapy comparisons.

CD4 count

Two studies compared different monotherapies[129; 130]; these were didanosine versus zidovudine, and lamivudine versus zidovudine. Zidovudine was taken as the standard control arm. Both favoured the alternative treatment arm, although only didanosine was found to be significantly more effective than zidovudine, with an increase of 71 cells per μl (95% CI 29, 114) over zidovudine.

Viral load

The viral load data also had two comparisons[129; 131] – lamivudine versus zidovudine, and saquinavir versus zidovudine. Lamivudine was significantly more effective than zidovudine, with a viral load reduction of 0.17 log copies per ml (95% CI 0.02, 0.32). Saquinavir was found to be significantly less effective than zidovudine.

Disease progression/death

Five studies contributed to three different comparisons with disease progression/death outcomes[129-133], although most of the information was a comparison of didanosine and zidovudine. None of the monotherapies were significantly different.

Adverse events

Adverse event data was available from two studies[129; 132]. The results showed that neither lamivudine nor didanosine showed significantly different rates of drug-related adverse effects compared with zidovudine.

Conclusions

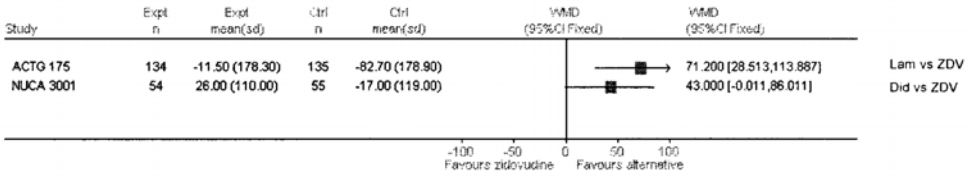
Although data from the surrogate markers suggest that didanosine is significantly (both statistically and probably clinically) more effective than zidovudine, uncertainty remains because this is not reflected by the disease progression data. Dropout due to drug-related adverse events shows no difference between monotherapies.

Table 14 Monotherapy comparisons * median †endpoint ‡ not contributing to combined result

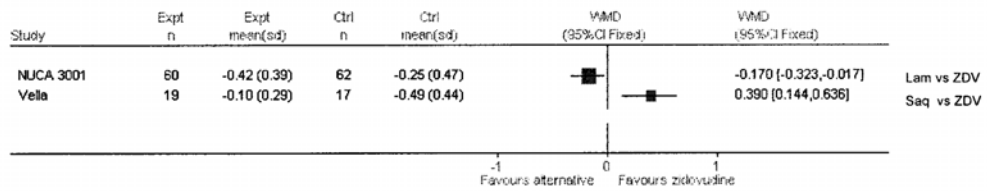
Trial identifier	*Duration of trial* *(weeks)*	*Treatment arm*					*Control Arm*				
CD4 count											
	Timepoint		***n***	***Baseline CD4 count*** *(cells per μl)*	***Mean CD4 change*** *(cells per μl)*	***SD***		***n***	*Baseline CD4 count* *(cells per μl)*	***Mean CD4 change*** *(cells per μl)*	***SD***
NUCA 3001[81]	48	Lamivudine	54	340	26	110	Zidovudine	55	349	-17	119
ACTG 175[47]	128	Didanosine	134	372	-11.5	178.3	Zidovudine	135	372	-82.7	178.9
Vella‡[80]	16	Saquinavir	19	173	3*	-	Zidovudine	17	168	0*	-
ISS 902‡[57]	26	Didanosine	118	-	76	-	Zidovudine	118	-	39	-
Viral load											
	Timepoint		***n***	***Baseline-VL*** *(log copies per ml)*	***Mean VL change*** *(log copies per ml)*	***SD***		***n***	***Baseline-VL*** *(log copies per ml)*	***Mean VL change*** *(log copies per ml)*	***SD***
NUCA 3001[81]	24	Lamivudine	60	4.5	-0.42	0.39	Zidovudine	62	4.6	-0.25	0.47
Vella[80]	16	Saquinavir	19	-	-0.1	0.29	Zidovudine	17	-	-0.49	0.44
Disease progression/death											
				Patients progessing (n)	***Patients entered (N)***				***Patients progessing (n)***	***Patients entered (N)***	
NUCA 3001[81]	52	Lamivudine		1	87		Zidovudine		3	93	
ACTG 175[47]	135	Didanosine		23	268		Zidovudine		32	269	
Vella[80]	16	Saquinavir		1	19		Zidovudine		2	17	
ISS 902[57]	87	Didanosine		73	279		Zidovudine		73	275	
ACTG 116A[48]	85	Didanosine		80	197		Zidovudine		40	106	
	85	Didanosine		89	208		Zidovudine		40	106	
Adverse events											
				Patients dropping out due to adverse events (n)	***Patients entered (N)***				***Patients dropping out due to adverse events (n)***	***Patients entered (N)***	
NUCA 3001[81]	52	Lamivudine		7	87		Zidovudine		11	93	
ISS 902[57]	87	Didanosine		48	279		Zidovudine		34	275	

Figure 9 Forest plot comparing different monotherapies

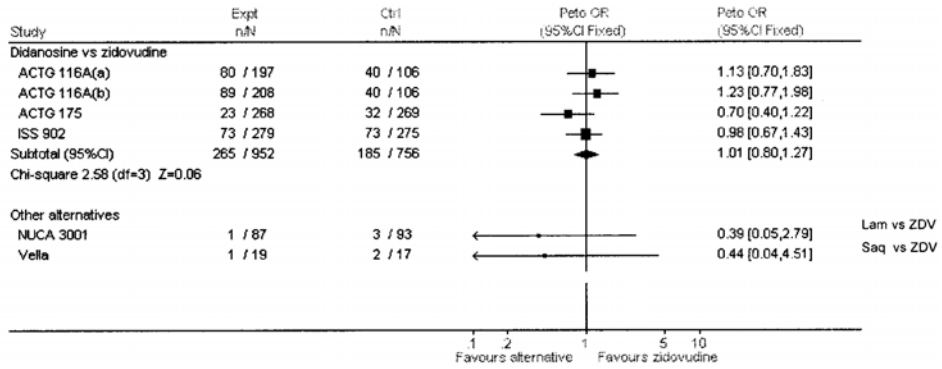
CD4 count



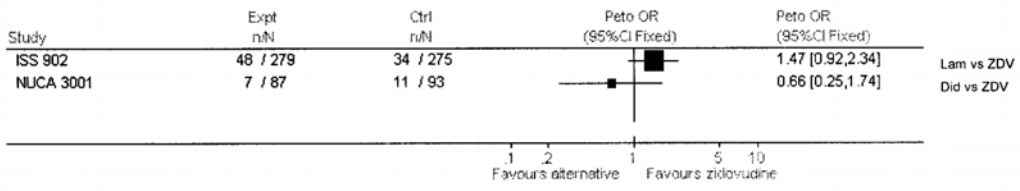
Viral load



Disease progression/death



Adverse events



9.4.2 Double therapy

Table 15 shows the results of double therapy comparisons.

CD4 count

There were fifteen comparisons which contributed to the CD4 results. Four studies compared zidovudine + zalcitabine with zidovudine + didanosine and five others compared other combinations with zidovudine + didanosine. The majority of the remainder compared different combinations with zidovudine + lamivudine.

The results are illustrated in figure 10, where comparisons are displayed in appropriate groupings. The data indicate that the efficacy of ZDV+Zalc is not significantly different to that of ZDV+Did, but that ZDV+Nev and ZDV+Del are significantly less effective. There was no direct comparison of ZDV+Lam against either ZDV+Did or ZDV+Zalc.

Viral load

The viral load double therapy comparisons are illustrated in a similar way in figure 9. 12 studies contributed to the results, including three studies comparing ZDV+Zalc with ZDV+Did, four with other combinations against ZDV+Did and two studies comparing Stav+Lam with ZDV+Lam.

The results show that ZDV+Zalc is significantly less effective than ZDV+Did (overall reduction in viral load 0.16 log copies per ml), ZDV+Nev is significantly less effective than ZDV+Did, Stav+Did is significantly more effective than ZDV+Lam, and that none of the other comparisons showed significant differences.

Disease progression/death

There were four results which compared ZDV+Zalc with ZDV+Did with a disease progression/death outcome (figure 10). The other two comparisons were against ZDV+did and ZDV+Lam. The results indicate that ZDV+Zalc is significantly less effective than ZDV+Did (combined OR = 1.4 (95% CI 1.13, 1.73)). The other two comparisons showed no difference.

Table 15 Double therapy comparisons

* median †endpoint ‡ not contributing to combined result

Trial identifier	*Duration of trial (weeks)*	*Treatment arm*					*Control Arm*				
CD4 count											
	Timepoint		***n***	***Baseline CD4 count (cells per μl)***	***Mean CD4 change (cells per μl)***	***SD***		***n***	***Baseline CD4 count (cells per μl)***	***Mean CD4 change (cells per μl)***	***SD***
ACTG 175[47]	128	ZDV+Zalc	132	372	34.6	157.3	ZDV+Did	134	372	50	220.6
EARTH-1[93]	52	ZDV+Zalc	14	597	83.6	112.8	ZDV+Did	15	621	146.3	129.1
DELTA-1[50]	80	ZDV+Zalc	426	213	-2.0*	159	ZDV+Did	435	214	17*	223
Protocol 34,225-02[84]	48	ZDV+Zalc	61	135	178†	161	ZDV+Did	59	147	157†	158
Foudraine[54]	12	Stav+Lam	23	290	115*	104	ZDV+Lam	24	315	110*	94
ACTG 306[59]	24	Stav+Lam	53	405	120.8	151.4	ZDV+Lam	49	401	84.4	127.4
INCAS[90]	52	ZDV+Nev	47	346	-6	65	ZDV+Did	52	390	87	151
ACTG 261[89]	48	ZDV+Del	101	295	-14	119	ZDV+Did	52	284	41	120
	48	Did+Del	108	305	25	123	ZDV+Did	52	284	41	120
A1455-053‡[87]	24	Stav+Did	57	314	115*	-	ZDV+Did	53	321	116	-
EARTH-1[93]	52	Stav+Did	16	662	146.3	133.5	ZDV+Did	15	621	146.3	129.1
ACTG 306[59]	24	Did+Lam	52	387	111.5	111.1	ZDV+Lam	49	386	87.2	107.8
ALBI[55]	24	Stav+Did	24	389	124	102.8	ZDV+Lam	24	421	62	116.5
	24	Alt Stav+Did/ZDV+Lam	24	403	118	117.8	ZDV+Lam	24	421	124	102.8
	24	Alt Stav+Did/ZDV+Lam	24	403	118	117.8	Stav+Lam	24	389	62	116.5
Viral load											
	Timepoint		***n***	***Baseline-VL*** *(log copies per ml)*	***Mean VL change*** *(log copies per ml)*	***SD***		***n***	***Baseline-VL*** *(log copies per ml)*	***Mean VL change*** *(log copies per ml)*	***SD***
DELTA-1[49]	16	ZDV+Zalc	108	4.74	3.66†	0.56	ZDV+Did	179	4.71	3.51†	0.75
EARTH-1[93]	-	ZDV+Zalc	14	4.6	-1.58	0.86	ZDV+Did	15	4.64	-1.67	0.75
Protocol 34,225-02[84]	48	ZDV+Zalc	61	5.1	4.53†	1.02	ZDV+Did	59	4.82	4.30†	1.0

Trial identifier	*Duration of trial* *(weeks)*	*Treatment arm*					*Control Arm*				
Foudraine[54]	12	Stav+Lam	23	4.98	-1.65*	0.63	ZDV+Lam	24	4.8	-1.53*	0.24
ACTG 306[59]	24	Stav+Lam	52	4.13	-1.07	0.81	ZDV+Lam	54	4.15	-0.84	0.87
INCAS[90]	52	ZDV+Nev	46	4.54	-0.22	0.25	ZDV+Did	51	4.47	-1.05	1.57
ACTG 261[89]	48	ZDV+Del	34	4.64	-0.4	0.62	ZDV+Did	19	4.3	-0.52	0.91
	48	Did+Del	46	4.41	-0.63	0.72	ZDV+Did	19	4.3	-0.52	0.91
EARTH-1[93]	-	Stav+Did	16	4.48	-1.81	0.78	ZDV+Did	15	4.64	-1.67	0.75
A1455-053‡[87]	24	Stav+Did	56	4.8	-1.5*	-	ZDV+Did	52	4.6	-1.6*	-
ACTG 306[59]	24	Did+Lam	44	4.08	-0.83	0.72	ZDV+Lam	53	4.01	-0.83	0.79
ALBI[55]	24	Stav+Did	23	4.46	-2.26	0.75	ZDV+Lam	23	4.57	-1.26	0.61
	24	Alt Stav+Did/ZDV+Lam	23	4.58	-1.58	0.88	ZDV+Lam	23	4.57	-1.26	0.61
	24	Alt Stav+Did/ZDV+Lam	23	4.58	-1.58	0.88	Stav+Did	23	4.46	-2.26	0.75
EARTH-1[93]	-	Stav+Did	16	4.48	-1.81	0.78	ZDV+Zalc	14	4.6	-1.58	0.86

Disease progression/death

			Patients progessing (n)	*Patients entered (N)*		*Patients progessing (n)*	*Patients entered (N)*
ACTG 175[47]	135	ZDV+Zalc	20	263	ZDV+Did	16	267
EARTH-1[93]	52	ZDV+Zalc	1	29	ZDV+Did	0	32
DELTA-1[50]	144	ZDV+Zalc	231	706	ZDV+Did	188	718
Protocol 34,225-02[84]	72	ZDV+Zalc	9	61	ZDV+Did	3	59
INCAS[90]	52	ZDV+Nev	11	47	ZDV+Did	13	53
ALBI[55]	24	Stav+Did	1	51	ZDV+Lam	0	51

Adverse Events

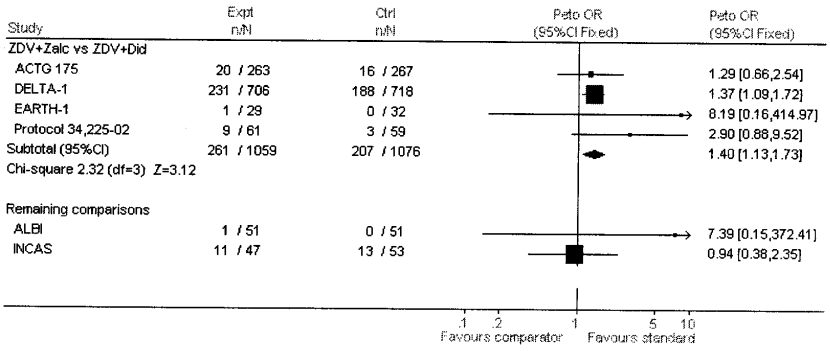
			Patients dropping out due to adverse events (n)	*Patients entered (N)*		*Patients dropping out due to adverse events (n)*	*Patients entered (N)*
EARTH-1[93]	52	ZDV+Zalc	3	29	ZDV+Did	7	32

Trial identifier	*Duration of trial* *(weeks)*	*Treatment arm*			*Control Arm*		
DELTA-1[50]	144	ZDV+Zalc	155	706	ZDV+Did	173	718
Protocol 34,225-02[84]	72	ZDV+Zalc	10	61	ZDV+Did	5	59
Foudraine[54]	12	Stav+Lam	0	23	ZDV+Lam	1	24
INCAS[90]	52	ZDV+Nev	12	47	ZDV+Did	7	53
ALBI[55]	24	Stav+Did	1	51	ZDV+Lam	2	51
A1455-053[87]	36	Stav+Did	6	67	ZDV+Did	5	70

Figure 10 Forest plot comparing double combinations

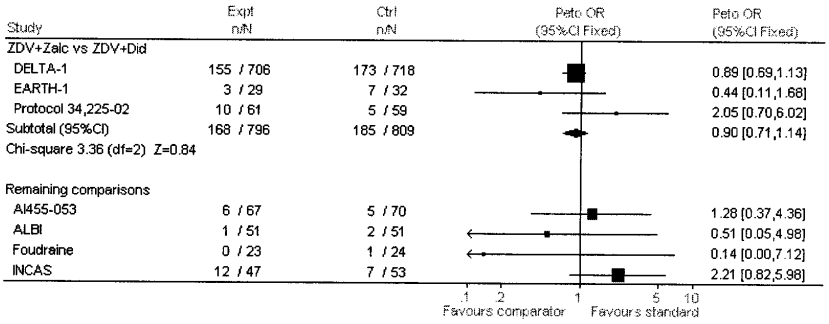
Figure 10 continued: Forest plot comparing double combinations

Disease progression/death



Stav+Did vs ZDV+Lam
ZDV+Nev vs ZDV+Did

Adverse events



Stav+Did vs ZDV+Did
Stav+Did vs ZDV+Lam
Stav+Lam vs ZDV+Lam
ZDV+Nev vs ZDV+Did

Adverse events

Seven results gave information on adverse events for four different comparisons. The data show that none of the double therapies produced significantly different rates of serious adverse events.

Conclusions

From the data, it is likely that all double combinations are similarly effective (with the possible exception that ZDV+Did is more effective than ZDV+Zalc). However, the data remain incomplete and inconsistent.

9.4.3 Triple therapy

Triple combination comparisons are given in table 16 and figure 11. Overall, there are few comparisons between different triple combinations; they are limited to ZDV+Lam+Ind, ZDV+Lam+Saq and ZDV+Lam+Efa.

CD4 count

One study shows that ZDV+Lam+Saq is significantly more effective than ZDV+Lam+Ind[52], and the other that there is no significant difference between ZDV+Lam+Ind and ZDV+Lam+Efa[92].

Viral load

The only study with results compared ZDV+Lam+Ind with ZDV+Lam+Saq[52], and reported that there was no significant difference in reduction of viral load, although no measure of variance or p values were given.

Disease progression/death

The disease progression data suggest that although the point estimate favours ZDV+Lam+Saq, this combination is not significantly more effective than ZDV+Lam+Ind. ZDV+Lam+Ind was not found to be any different from ZDV+Lam+Efa.

Adverse events

The adverse event data, although with wide confidence intervals, do not show any statistical difference between the different triple therapies compared.

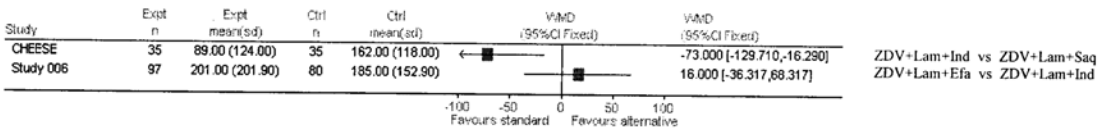
Table 16 Triple therapy comparisons

* median †endpoint ‡ not contributing to combined result

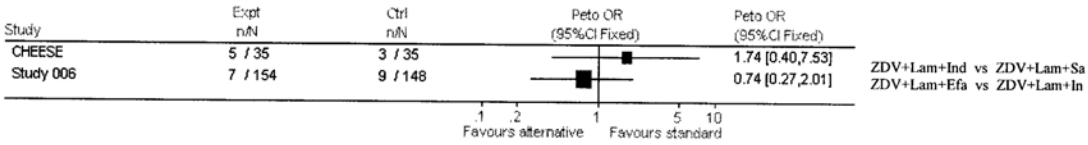
Trial identifier	*Duration of trial (weeks)*	*Treatment arm*					*Control Arm*				
CD4 count											
	Timepoint		***n***	***Baseline CD4 count*** *(cells per µl)*	***Mean CD4 change*** *(cells per µl)*	***SD***		***n***	*Baseline CD4 count (cells per µl)*	***Mean CD4 change*** *(cells per µl)*	***SD***
CHEESE[52]	24	ZDV+Lam+Ind	35	310	89	124	ZDV+Lam+Saq	35	301	162	118
Kirk‡[46]	24	Rit+2NAs	42	111	117*	-	Ind+2NAs	38	91	132*	-
Study 006[92]	48	ZDV+Lam+Efa	97	350	201	201.9	ZDV+Lam+Ind	80	341	185	153
Viral load											
	Timepoint		***n***	***Baseline-VL*** *(log copies per ml)*	***Mean VL change*** *(log copies per ml)*	***SD***		***n***	***Baseline-VL*** *(log copies per ml)*	***Mean VL change*** *(log copies per ml)*	***SD***
CHEESE‡[52]	24	ZDV+Lam+Ind	29	4.98	-2.38*	-	ZDV+Lam+Saq	31	5.0	-2.40*	-
Disease progression/death											
				Patients progessing (n)	***Patients entered (N)***				***Patients progessing (n)***	***Patients entered (N)***	
CHEESE[52]	24	ZDV+Lam+Ind		5	35		ZDV+Lam+Saq		3	35	
Study 006[92]	48	ZDV+Lam+Efa		7	154		ZDV+Lam+Ind		9	148	
Adverse events											
				Patients dropping out due to adverse events (n)	***Patients entered (N)***				***Patients dropping out due to adverse events (n)***	***Patients entered (N)***	
CHEESE[52]	24	ZDV+Lam+Ind		2	35		ZDV+Lam+Saq		0	35	
Study 006[92]	48	ZDV+Lam+Efa		10	154		ZDV+Lam+Ind		9	148	

Figure 11 Forest plot comparing triple therapies

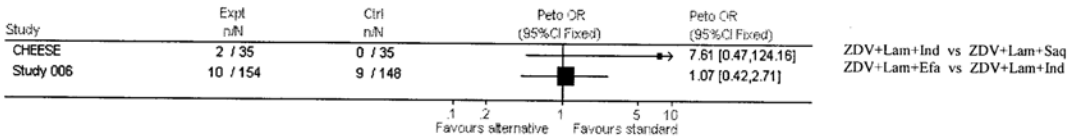
CD4 count



Disease progression/death



Adverse events



Conclusions

The data are very limited, but both the CD4 and viral load data, and the direction of the disease progression data, are consistent with ZDV+Lam+Saq being more effective than ZDV+Lam+Ind. ZDV+Lam+Efa may be equally effective as ZDV+Lam+Ind.

9.4.4 Quadruple therapy

No data were available which compared different types of quadruple therapy.

Summary Box 4: Effectiveness of particular combinations of antiretroviral therapy

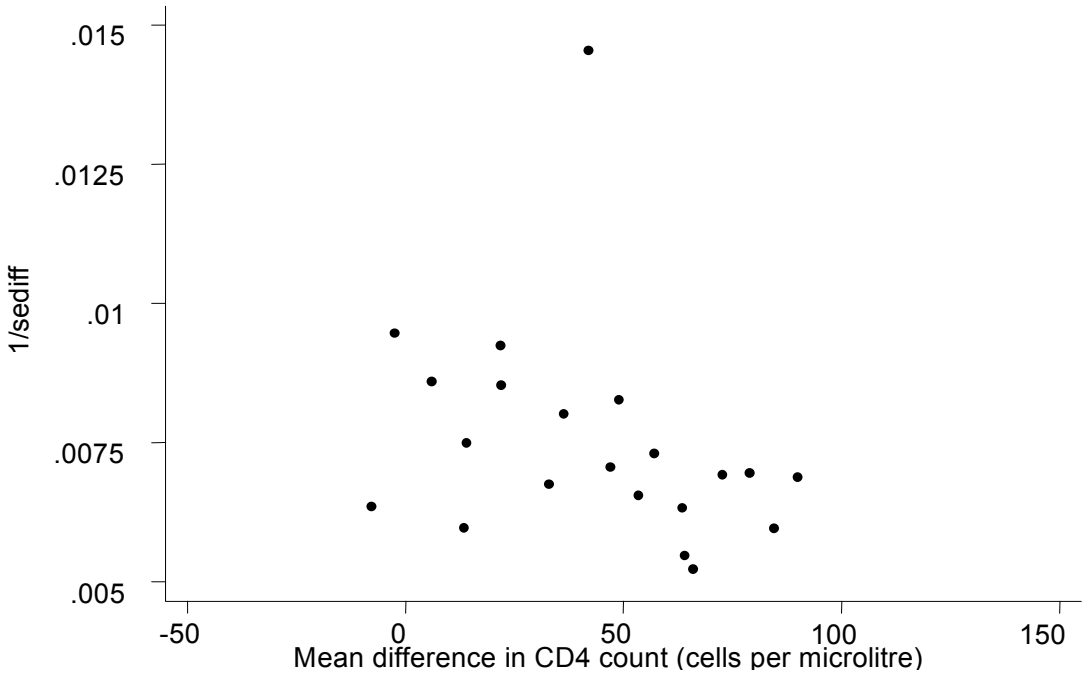
- Data available were frequently incomplete, with only a limited number of the possible combinations compared.
- Zidovudine and didanosine were the most frequent monotherapies to be compared. Uncertainty remains about their comparative effectiveness (although didanosine may be more effective), but the rates of serious adverse effects leading to withdrawal were similar.
- The most frequent double combinations to be compared were ZDV + Zalc with ZDV + Did. There were no direct comparisons between ZDV+Did and ZDV+Lam. No conclusions could be drawn about the relative effectiveness of different combinations as the data were inconsistent. Adverse event withdrawal rates did not differ between different combinations.
- Few triple combinations were compared directly. There was no significant difference in adverse event-related withdrawal rates.

9.5 Publication bias

Publication bias was assessed by means of a funnel plot (figure 12), using CD4 count in the double versus monotherapy comparison as it had the greatest number of data points. The plot shows a measure of variance against effect size (therefore includes only the 21 points for which SD data was available). Visual inspection suggests that the plot is symmetrical, however two statistical tests were performed to assess the extent of any asymmetry. Egger's test suggested that any asymmetry was non-significant (p=0.18), although Begg's test showed the reverse (p=0.027). There is continuing debate about the value of these tests (Personal Communication. Preston, C.), and some statisticians argue that visual inspection is most useful. In addition, publication bias may not always be the cause of asymmetry. Taken together, although publication bias might seem unlikely, it cannot be excluded.

The greatest likelihood of publication bias is likely to be in the more recent publications, particularly in the triple versus double therapy comparison group. The limited number of data points precluded any meaningful assessment of publication bias in this group.

Figure 12 Funnel plot to illustrate potential publication bias: change in CD4 count (double therapy versus monotherapy)



10 Costs of antiretroviral therapy and HIV/AIDS

10.1 Drug costs

Table 4 [Anti-retroviral drugs currently available (licensed by FDA)] gives the individual weekly drug costs, if standard doses are employed, for the antiretroviral drugs currently available. These range from c £35 to £95 per week. In general the well established NRTI's eg zidovudine, lamivudine, zalcitabine and didanosine tend to be at the lower end of this range and newer drugs in the protease inhibitor class eg saquinavir and ritonavir at the upper end.

When starting treatment the recommended triple combinations are 2 NRTI's + PI or 2 NRTI's + NNRTI or 3 NRTI's. The cost of starting antiretroviral therapy in naïve patients might range from c £110 per week (eg zidovudine + zalcitabine + nevaripine) to £190 (stavudine + abacavir + ritonavir). The upper limit might be increased slightly to c £200 per week if a second low dose PI (usually ritonavir 100-400mg daily) is added to a 2 NRTI + PI regime for pharmacokinetic reasons. Based on this, *if* the most expensive combinations were currently being used, annual treatment costs might be reduced from £10,400 to £5,700 per year by using recommended combination therapies composed of the *least expensive* agents. This potential saving would however be considerably off-set by having to use more expensive agents, avoided initially, in combination therapy once the first regime had failed.

In addition to the direct drug costs, the following costs also need to be considered:

- Costs associated with additional monitoring of renal and hepatic function, impairment of which is associated with many antiretroviral agents. The additional costs associated with this are difficult to quantify as there will be uncertainty about the degree to which such routine blood tests might be employed in the care of a patient with HIV irrespective of whether they are on treatment.
- Costs associated with additional monitoring of CD4 counts and plasma viral load – the approximate cost of the latter is £50 per test.
- Costs associated with the need for resistance testing, estimated to be £350 per patient on antiretroviral therapy per year.

On this basis, at least £500 per patient per year should probably be added to the direct drug costs to reflect the true increase in cost associated with providing currently recommended combinations of antiretroviral therapy.

The total cost to the West Midlands associated with antiretroviral therapy can be estimated by applying the costs above to the number of patients thought to be eligible for antiretroviral therapy. In 2000 this is approximately 450, including both patients who have only had one type of triple therapy and others who are on salvage therapy after their first or subsequent combinations have failed. On this basis the total expenditure on drugs and directly related additional costs could range from £2.8 m per annum if the cheapest drugs were being used, to £4.9 m per annum if the most expensive were being used. The actual value is likely to lie between these two. This assumes that the complexity of

regimes used in naïve patients is similar to the complexity of regimes used subsequently. If current recommendations are adhered to this will generally be true.

An important point to note is that for the near future, the total cost of antiretroviral drugs is likely to grow substantially even if the recommendations on optimal combination therapy and individual agent costs remain unchanged. This is because the incidence of new cases of HIV (c 80-100 per year in the West Midlands over the period of 1990-1998) is greatly in excess of deaths from AIDS (c 10 per year in the West Midlands in 1998), the latter having fallen considerably since 1996.

10.2 Wider costs

A comprehensive review of the health economics of HIV disease over the period 1985-1998 included a review of resource use and cost studies[135]. European observational studies on resource use and costs showed reductions of 35-40% in hospital admissions, new AIDS cases and mortality following the introduction of combination therapy. The review concludes that "combination therapies appear to be successful in reducing disease progression and the healthcare resources required", but that "long term data are needed to determine whether this reduction in resource use can be sustained or whether it is transient".

Many of the European studies reviewed reported resource use stratified by disease severity, but the main source of cost estimates by disease stage used to model lifetime costs of HIV and AIDS remains the 1992 US study by Hellinger.[134] This estimated the monthly healthcare charges (in 1992 US dollars) of treating a person with HIV at $282 for CD4 count above 500, $430 for CD4 count 200-500, $990 for CD4 count below 200 and $2764 for a person with AIDS. Using 1992 estimates of disease progression, the cost of care during HIV above CD4 500 was $19,000 (5.6 years); at CD4 200-500 was $18,900 (3.7 years); at CD4 below 200 was $12,300 (one year); and at AIDS was $69,100 (two years). The total lifetime cost of care (undiscounted) was $119,300.

Updates of these estimates based on treatments and associated resource use and survival rates in 1996 put the annual cost of HIV at CD4 above 500 at $9,303 to $16,167 depending on treatment used, at CD4 200-500 $8,108 to $17,835, at CD4 below 200 at $16,002 to $25,729 and at AIDS $39,283 to 49,010[140]. Duration in the last two stages is assumed to remain at one and two years respectively, but duration at earlier stages is increased according to treatment used. The total lifetime cost of care (undiscounted) is estimated at $274,766 to $424,763 depending on treatment strategy. Survival in these updated estimates rises to between 16 and 21years due to newer treatment strategies so discounting has a significant effect on the present value of lifetime costs: at 3% discount these are $195,188 to $296,844.

11 Economic evaluation of antiretroviral therapy

No economic evaluations were identified from the systematic review which reported effectiveness and resource use data collected in the context of a randomised controlled trial of one combination of antiretroviral therapy versus another in treatment-naïve patients. However, many retrieved articles reported economic evaluations of antiretroviral therapy in people with AIDS and in treatment-experienced or mixed groups of people with HIV infection.

This section draws on this pool of potentially relevant studies. The published literature on cost-effectiveness of antiretroviral therapy for HIV infection is reviewed and key issues are highlighted.

Although these studies could not be included in the systematic review of antiretroviral therapy for HIV infection in treatment-naïve patients reported above, it is hoped that the review presented here provides useful information for decision-makers on the potential cost-effectiveness of antiretroviral therapy.

11.1 Methods

11.1.1 Search strategy

In addition to the included studies reported in the previous sections, all retrieved studies were assessed for their potential relevance for informing economic evaluation sections of the review.

Citations were retrieved through the search strategy of the systematic review reported in section 9.2 above. This strategy did not aim to capture all studies of economic aspects of HIV and AIDS, only those related to the comparative evaluation of different combinations of antiretroviral therapy in treatment-naïve patients. As such, the economic literature reviewed in this section is not intended to be exhaustive. A comprehensive review of the health economics of HIV disease over the period 1985-1998 has been conducted by the HIV Health Economics Collaboration, the European results of which are available and the North American results forthcoming[135]. This review documents studies of resource use and costs, burden-of-illness and planning and economic evaluations of treatments for opportunistic infections as well as evaluations of antiretroviral therapy for HIV infection. Five economic evaluations of antiretroviral therapy are covered in the review of European literature[135] of which three were available only in abstract form; the two published evaluations are included in the studies reviewed here. The review of European literature highlighted the paucity of thorough economic studies of HIV disease and its treatment and noted the difficulties for economic evaluation raised by the absence of standardised cost frameworks, the use of many different aspects of the healthcare sector and the reliance on surrogate end-points in clinical trials.[135] The review concluded that economic evaluations show "treatments available are attractive in terms of their cost-effectiveness".[135]

11.1.2 Quality assessment and data extraction

The retrieved articles reporting economic evaluation of antiretroviral therapy for HIV infection were reviewed against published quality criteria.[136] Quality assessment and data extraction were conducted independently by two reviewers and any discrepancies were resolved through discussion. The key characteristics and findings of all reported economic evaluations retrieved were summarised.

11.2 Search results

No included studies presented economic evaluation reporting effectiveness and resource use data collected in the context of a randomised clinical trial of one combination of antiretroviral therapy versus another in treatment-naïve patients.

Other studies of potential relevance included 20 articles relating to economic evaluation of antiretroviral therapy for adult HIV infection, 21 articles relating to other economic evaluations within the HIV field or reviews of economic evaluation in HIV and AIDS, 38 articles reporting health-related quality of life assessment in adults with HIV infection, and 58 articles reporting resource use and costs associated with HIV infection.

11.3 Characteristics of economic evaluations of antiretroviral therapy

The characteristics of the twenty economic evaluations are presented in Tables 17a and b. Five studies presented economic evaluations based on observational data only; three used hospital or registry databases as the source of resource use and outcome data and two used data collected in the course of a randomised controlled trial. The remaining fifteen studies used a modelling approach based on data from observational studies, clinical trials and/or estimates from the literature and/or expert opinion. All used models to estimate the cost-effectiveness of one form of antiretroviral therapy compared to another. Models were used both to extrapolate from the short-term results of clinical trials and/or observational studies to lifetime costs and outcomes, and to combine effectiveness and cost data from alternative sources.

The proportion of studies that used a model-based approach illustrated the difficulty of interpreting cost-effectiveness results from limited-duration trials. Clinical trials of one year duration can only provide cost-effectiveness information in terms of one-year outcomes, such as cost per progression avoided in one year.[137] This outcome measure is of little meaning if the implications for lifetime outcomes and costs cannot be inferred, and the cost-effectiveness of therapy expressed in such terms cannot be compared to the use of healthcare resources in other clinical areas. The benefit of model-based economic evaluations in HIV and AIDS is therefore to be able to assess lifetime costs and outcomes with alternative therapy combinations and to express the cost-effectiveness of one alternative over another in terms of cost per life year gained or cost per quality-adjusted life year (QALY) gained.

A good example of the format of a model-based economic evaluation is detailed in box 1.

Box 1: Modelling the cost-effectiveness of HAART[138]

Model
Semi-Markov model describes the natural history of a person with HIV infection passing through three states ("No AIDS", "AIDS", "Dead") over a sequence of 6-month intervals until death. Each of the three broad states is sub-divided into CD4 count strata of CD4 0-199, CD4 200-499 and CD4>500.

Effects
Transition rates within each state between CD4 strata and between states were calculated from cohort study data on people taking no therapy and HAART respectively. Cohort study data also provides information on ability to work and hours worked. Lifetime outcomes are simulated by following 30,000 individuals through the model until death in both strategies (Monte Carlo simulation).

Costs
Health care costs were estimated from a random sample of people enrolled in the cohort study followed up at one HIV clinic. Costs were matched to disease stage and CD4 strata and included antiretroviral and prophylactic drugs, all medical interventions and consultations. Productivity estimates were calculated by assigning the average Swiss hourly wage to estimates of hours worked. Lifetime costs were simulated by the same cohort simulation of 30,000 individuals used to estimate survival.

Incorporating uncertainty
Due to a lack of evidence on the long-term effects of HAART, pessimistic and optimistic scenarios were constructed for transition rates between states for people on HAART using the 2.5 and 97.5 percentile of distributions based on maximum likelihood estimates.

Results
From a societal perspective (i.e. including productivity effects) HAART compared to no treatment is associated with an additional survival of 4.6 to 13.7 years and additional costs of up to 50,500 CHF, producing an incremental cost-effectiveness ratio that ranges from cost-saving to 11,000 CHF per life-year gained. From a health care perspective, additional survival is estimated to be 4.3 to 11.7 years and additional costs 168,000 to 201,870 CHF, producing an incremental cost-effectiveness ratio of 14,000 CHF to 45,000 CHF per life year gained ranges.

[£1 ≅ 2.5 CHF]

Later studies have benefited from the increased availability of evidence on the effect of HIV/AIDS and of antiretroviral therapy on health-related quality of life. Such evidence allows economic evaluation to move from cost-effectiveness analyses using life-years gained as the primary outcome measure to cost-utility studies assessing additional cost per quality-adjusted life year gained[139], [140]. In turn, this allows the comparison of the value of funding new treatments in HIV to be compared to other new health care technologies.

11.3.1 Monotherapy versus no treatment

The comparators assessed in the economic evaluations reflect technological developments over time. The three studies based on hospital or registry data were conducted in the late 1980s and compared the resource use and outcomes of people with AIDS receiving zidovudine monotherapy to people with AIDS not receiving

zidovudine.[141, 142, 143] The four earliest models also evaluate the effectiveness of zidovudine monotherapy, compared either to no antiretroviral treatment [144, 145, 146] or to delayed zidovudine monotherapy.[147]

11.4 Double therapy versus monotherapy

One published study presented an economic evaluation conducted alongside a randomised controlled trial of dual NRTI therapy versus monotherapy and discussed the necessary direction for future economic evaluation of antiretroviral therapy.[137, 148, 149, 150]

Three modelling studies have specifically addressed the cost-effectiveness of dual therapy versus monotherapy [151, 152, 139] and a fourth study included a comparison of double versus monotherapy.[140]

11.4.1 Triple therapy versus double therapy (or monotherapy, or no treatment)

The other study which presented an economic evaluation conducted alongside a clinical trial is available only in abstract form and assessed the impact of the addition of ritonavir versus placebo to current antiretroviral therapy on the occurrence of opportunistic infections and associated healthcare resource use.[153]

Finally, eight studies published in the latter half of the 1990s modelled the cost-effectiveness and/or cost-utility of triple combination therapy versus triple[154], dual [140, 155, 156] or monotherapy [157, 158, 159] and versus no treatment.[138]

The comparisons evaluated vary, and raise the important question for cost-effectiveness analysis of the appropriate comparator to be used. Studies that assess different treatments and against different comparators are not strictly comparable, and the results of the studies reviewed here are perhaps more useful in illustrating general themes and issues to be considered.

11.5 Quality of economic evaluations of antiretroviral therapy

The results of the quality assessment are shown in Table 19. Studies varied in quality and there was some trend in improvement in the quality of reporting of economic evaluations over time.

11.5.1 Monotherapy versus no treatment

The time at which studies were conducted is associated with the quality of reporting of the economic evaluation. For example, the three studies based on hospital or registry data did not fulfil many of the accepted quality criteria for economic evaluation studies, however, these studies were conducted before such criteria were published.[136] The quality of the three studies that modelled the cost-effectiveness of zidovudine monotherapy against no treatment is equally weak when assessed against the 1996 guidelines, although the study of immediate versus deferred zidovudine appears to be of higher quality.[147]

11.5.2 Double therapy versus monotherapy

The published study of economic evaluation conducted alongside a randomised controlled trial was of high quality and presented a comprehensive analysis of the cost-effectiveness of dual NRTI therapy vs monotherapy.[137, 148, 149, 150]. The quality of model-based evaluations of double versus monotherapy showed some variation, with the two of the studies published after 1996 [152, 139] satisfying more of the 1996 quality criteria than the earlier study,[151] although all four studies in this group satisfied over two-thirds of the applicable quality assessment criteria.

11.5.3 Triple therapy versus double therapy (or monotherapy, or no treatment)

The study which presented an economic evaluation conducted alongside a clinical trial was available only in abstract form and the information presented did not allow the quality of this study to be fully assessed.[153]

The quality of studies that estimated the cost-effectiveness of HAART varied considerably. Several studies in this group presented brief analyses estimates in the discussion section of the article as preliminary or speculative estimates of cost-effectiveness. These estimates were not supported by detailed analysis in the paper as economic evaluation of combination antiretroviral therapy was not the main focus of the article.[140, 155, 157, 158, 159] Other modelling studies presented comprehensive economic evaluations that met most of the applicable quality assessment criteria.[138] Again, there is some indication of a rising trend in the quality of reporting of economic evaluations over time, as assessed by the BMJ quality criteria.

11.6 Findings of economic evaluations of antiretroviral therapy

The key results of the twenty economic evaluations are shown in Table 17a and b.

11.6.1 Monotherapy versus no treatment

Three studies based on hospital or registry data compared the resource use and outcomes of people with AIDS receiving zidovudine monotherapy to people with AIDS not receiving zidovudine. The two US studies estimated zidovudine to be associated with an additional charge of $16,000 and $34,600 per life year gained compared to no antiretroviral therapy.[141], [142] The London study estimated the additional cost per life year gained at £7,400.[143]

Four studies published in the early 1990s modelled the cost-effectiveness of zidovudine monotherapy, compared to either no antiretroviral treatment or to deferred zidovudine therapy. These models highlighted the sensitivity of results to model assumptions, in particular: duration of effect assumed, inclusion of productivity effects and inclusion of

effect on health-related quality of life of effects and side-effects of treatment. For example, Schulman estimated the additional cost per life year gained at $6,553 if treatment effects persisted but $70,526 if the benefit of zidovudine lasted only one year.[144] Other studies showed that zidovudine therapy is cost-saving compared to no treatment if the model used includes effects on labour productivity[146] and/or behavioural change.[145] Whilst the relevance of the comparisons presented in these early models has become outdated, the issues raised by the sensitivity of models to key assumptions remain relevant today. The study of early versus deferred zidovudine found an additional cost of $10,750 per additional month without AIDS, which was deemed not cost-effective. If side-effects reduced health-related quality of life by even 8%, any survival gains would be outweighed by decreased HRQL.[147]

11.6.2 Double therapy versus monotherapy

The study of the addition of lamivudine to zidovudine-containing treatment regimens in people with HIV infection was limited to a one year time frame. The authors found an additional cost per progression avoided in one year of £7,000-20,000 using United Kingdom cost estimates and similar results using German and Canadian cost estimates.[137], [148] However, as double therapy was associated with lower hospital inpatient admissions, when the relatively high healthcare costs of the United States were applied to trial data the healthcare resources saved through reduced inpatient care completely offset the additional drug costs involved.[149] The time frame of this study necessitated the use of the outcome measure of cases of progression avoided and as such the results of this study cannot be easily compared to model-based analyses which presented the additional cost per life year or quality-adjusted life year gained.

Model-based evaluations of double therapy versus monotherapy found double therapy to be associated with an additional cost per life year gained of £6,000-12,500 or $12,000-55,000. One study estimated an additional cost per QALY gained of $10,600-37,000.[139] Despite the difficulties of comparing results from studies using different comparators and different modelling assumptions, it was argued that these ranges of estimates compared favourably to some activities currently provided by public health care systems.

11.6.3 Triple therapy versus double therapy (or monotherapy, or no treatment)

Model-based evaluations of the cost-effectiveness and/or cost-utility of triple combination antiretroviral therapy produced estimates in a similar range to those found in the model-based evaluations of double versus monotherapy. Again, results were shown to be highly sensitive to model assumptions concerning the duration of treatment benefit.[156] Some studies were restricted to a limited time frame[155] or presented only a partial analysis.[153] Other studies presented preliminary or speculative estimates.[157], [158], [159] The higher quality or more comprehensive analyses reported cost-effectiveness estimates in the range £4,500-20,000 per life year gained.[156], [138] Studies that assess different treatments and against different comparators are not strictly comparable, although again the results fall within a range that, whilst not cost-neutral or "cheap" in terms of

additional resources required per life year or QALY gained, may compare favourably with some activities currently provided by public health care systems.

There appears to be an increase over time in the agreement between studies concerning the range within which cost-effectiveness estimates lie. This is perhaps not surprising given increased agreement on the duration of treatment effect. The majority of lifetime costs associated with HIV and AIDS is associated with the final years of life, spent in the final stages of the disease.[140], [134] So long as new antiretroviral treatments and therapy combinations only delay rather than prevent disease progression, the bulk of lifetime costs will be delayed rather than avoided. Discounting will make these future costs appear smaller as they are pushed further into the future, but balanced against this will be the immediate and ongoing additional cost of increased drug combinations. The result is that on comparison to lower combinations or indeed to no therapy, HAART results in increased lifetime outcomes (AIDS-free survival and associated HRQL, survival) and increased lifetime costs.

11.7 Issues in the assessment of cost-effectiveness of antiretroviral therapy for adults with HIV infection

The above review of economic evaluations of antiretroviral therapy for adults with HIV infection and AIDS has raised a number of considerations for future evaluations in this field.

11.7.1 Appropriate comparators

Economic evaluations are most useful for decision makers wishing to assess whether the benefits offered by a new technology are worth the additional expense. The question addressed must therefore relate to both the new technology and the comparator technology of interest. For new patients commencing antiretroviral therapy now, the most appropriate comparison would be between HAART and no treatment, rather than triple *versus* double therapy. For future policy, if higher combinations are proposed, the appropriate evaluation would be a comparison of triple *versus* higher combinations.

11.7.2 Duration of trials and duration of effect

The economic evaluation studies reviewed above illustrate a common sensitivity to assumptions concerning the duration of treatment effect. In the early 1990s, clinicians and health care policy makers were optimistic for the benefits of antiretroviral therapy, with the promise that the stream of new technologies could prevent the progression of disease. By the end of the century, such expectations had been tempered by evidence of limited duration of effect with the rise of drug resistance and rebound in viral load.

On the other hand, the 1990s saw an increasing number of clinical trials terminated early following evidence of benefit of one therapy arm (typically of higher-combination therapies over lower-combination comparators). The benefit of antiretroviral therapy, in turn, has led to increased survival of people with AIDS and the demonstration of

increased AIDS-free survival of people with HIV infection. These factors lead us to a situation at the end of the century where trials with clinical endpoints are seen as unethical and, in terms of the research resources required, not cost-effective research.

The combination of inevitably short-term trials and the need for consideration of duration of treatment effect leads to two conclusions for economic evaluation of antiretroviral therapy for HIV infection. The first is the inevitability of the use of modelling in economic evaluation studies. The second is the need for high quality observational studies to support or refute the assumptions of models concerning duration of treatment effect.

11.7.3 Scope of costs and benefits to be assessed

The majority of economic evaluations in HIV and AIDS have been conducted from the perspective of the health care provider or third-party payer. This has led most studies to exclude many categories of cost and benefit from economic evaluation. Studies that have attempted to include the indirect costs of HIV and AIDS in terms of lost productivity of people affected have demonstrated the sizeable impact this has on cost-effectiveness results.[146], [138] Because the population affected by HIV is of working age, and the number of working-age years lost to the disease is high, any inclusion of productivity will have a large impact on results. In most cases, the inclusion of effects on ability to work, hours worked, etc. will overwhelm the additional costs arising from more expensive drug treatments and any additional healthcare resource use, if found. The result is that new antiretroviral therapies are, from a societal perspective, cost-saving. The relevance of this result needs to be considered in view of the decision-makers concern for health care budgets and health care resource allocation.

The inclusion of health-related quality of life effects is increasingly important as information on HRQL becomes available in improved quantity and quality. Only by shifting the outcome of interest in economic evaluation from life-years gained to quality-adjusted life-years gained can researchers attempt to consolidate concerns of drug toxicity and patient concerns around treatment compliance, with overall notions of the value of therapy options.

Summary Box 5: Economic evaluation

- No economic evaluations were identified which reported effectiveness and resource use data collected in the context of a randomised controlled trial of one combination of antiretroviral therapy versus another in treatment-naïve patients.

- Other economic evaluations of antiretroviral therapy included five evaluations based on observational study data and fifteen model-based evaluations. Models were used to extrapolate from short-term results to lifetime costs and outcomes and to combine effectiveness and cost data from alternative sources.

- Results of economic analysis are sensitive to the perspective taken. In particular, including productivity effects has a large effect because people affected by HIV and AIDS are of working age.

- Cost-effectiveness results for more comprehensive model-based evaluations of triple therapy were in the range £4,500 to £20,000 per life year gained.

- Uncertainty around cost-effectiveness estimates cannot be reduced until high quality observational study data is available to provide a more certain basis on which to extrapolate from short-term trial results to lifetime costs and outcomes.

Table 17a - Characteristics of studies: economic evaluations alongside RCTs or using observational data only

First Author	Year	Publication	Therapy compared	Location	Form of analysis	Source of effectiveness data	Source of cost data
Monotherapy versus no treatment							
Scitovsky	1990	JAIDS	ZDV vs no treatment	San Francisco, USA	Observational study	San Francisco General Hospital & UCSF AIDS Registry	San Francisco General Hospital & UCSF AIDS Registry
Moore	1994	JAIDS	ZDV vs no treatment	Maryland, USA	Observational study	Maryland AIDS registry	Maryland AIDS registry
Beck	1996	Intl J STD & AIDS	ZDV vs no treatment	London, UK	Observational study	St Mary's Hospital records	St Mary's Hospital records
Double therapy versus monotherapy							
Lacey	1999	Pharmaco-economics	ZDV+Lam vs ZDV	UK & Germany / Canada / (US)	RCT	CAESAR (progression, OI & MOS-HIV show similar results)	CAESAR, Unit costs separately by country (& US unit costs applied to trial resource use data)
Triple therapy versus double therapy							
Brown	1996	Abstract	Rit vs P added to current therapy	USA	RCT	M94-247	M94-247

Table 17b - Characteristics of studies: economic evaluations using models

First Author	Year	Pub. Source	Therapy compared	Location	Form of analysis	Source of effectiveness data	Source of cost data
Monotherapy versus no (or deferred) treatment							
Oddone	1993	BMJ	ZDV vs deferred ZDV	USA	Markov model	RCT 1987-1991	RCT 1987-1991
Schulman	1991	Annals of Int. Med.	ZDV vs no treatment	USA	Model	ACTG019, epidemiologic model of survival	ACTG019, expert opinion
Paltiel	1991	JAIDS	ZDV vs no treatment	USA	Model	Estimates; includes ZDV effect, transmission & screening	Estimates
Meyer	1994	Applied Economics	ZDV vs no treatment	S. Africa, Johannesburg	Model	Cohort, 1988-1993	Cohort, 1988-1993
Double therapy versus monotherapy							
Simpson	1994	Pharmaco-economics	ZDV+Zalc vs ZDV	Europe	Markov model	ACTG114, ACTG106 & unpublished data	Estimates - Delphi process
Chancellor	1997	Pharmaco-economics	ZDV+Lam vs ZDV	UK, London	Markov model	Cohort of 4603 patients at 1 hospital, 1987-1995	Cohort of 389 AZT users, 1994-1995
Mauskopf	1998	Am. Jnl. Man Care	ZDV+Lam vs ZDV	USA	Markov model	Two trials for AZT/3TC, Hellinger for natural transition rates	Hellinger
Triple therapy versus double therapy (or monotherapy, or no treatment)							
Messori	1997	Annals of Pharmaco-therapy	ZDV+Zalc+Saq vs ZDV	USA	Extrapolated Q-TWiST model	Saravolatz et al (AZT), triple therapy modelled	Hurley et al (AZT), drug costs (triple)
Moore	1996	Pharmaco-economics	ZDV+Lam+Ind vs ZDV	USA	Model	Literature for AZT progression rates; estimates for triple based on VL/CD4 changes in trials	Hellinger for AZT lifetime costs; ART drug costs & VL test costs
Haburchak	1997	The AIDS Reader	Triple vs. mono-therapy	USA	Model	Estimates: SA of survival gain 0/6/36 months	Hellinger plus drug costs
Holtgrave	1997	JAIDS	ZDV vs ZDV+Lam vs ZDV+Lam+Saq	USA	Model	Survival assumptions plus synthesis of HRQL literature	Updated Hellinger & Gable costing
Anis	1998	Pharmaco-economics	PI+NRTIs vs NRTIs	Canada	Model	1-year survival benefit from ACTG 320	British Columbia observational database
Sendi	1999	AIDS	HAART vs no treatment	Switzerland	Semi-Markov model	Swiss HIV Cohort Study	Swiss HIV Cohort Study
Cook	1999	AIDS Res. & Human Retroviruses	ZDV+Lam+Ind vs ZDV+Lam	USA	Model	Transition rates from experts & Multicentre AIDS Cohort Study. Applied to subset of Merck 035	Daily costs by CD4 from Hellinger. Drug costs from US wholesale prices.
Williams	1999	CHERA Conference Abstracts	ZDV+Lam+Efa vs ZDV+Lam+Ind vs Ind+Efa	Canada	Model?	DMP-266-006	HIV Ontario literature + clinic data + experts

Table 18 - Key findings of economic evaluation studies

First Author	Year	Key findings
Monotherapy versus no (or deferred) treatment		
Scitovsky	1990	From AIDS diagnosis, mean survival 96.3 vs 45.5 weeks. Mean charges in 12 months $22,472 vs $41,133. Tentative ICER $16,000 (charge) per LYG.
Moore	1994	From AIDS diagnosis, median incremental charge per LYG $34,600 (mean $48,800) for AZT versus no treatment.
Beck	1996	From AIDS diagnosis, median survival 23 vs 13.5 months. Discounted cost per AIDS patient-year £13,495 vs £10,434. Therefore ZDV versus no treatment provides 9.5 months additional survival at extra cost per patient £5,865.
Oddone	1993	$10,750 per additional month without AIDS - not cost effective. Even a 8% decrease in health-related quality of life due to side-effects would render treatment arms equal.
Schulman	1991	$70,526 per additional life year if treatment effect lasts one year, $6,553 per life year if treatment effect continuous. Compares favourably with other medical therapies.
Paltiel	1991	If ZDV prolongs AIDS-free survival 1.5yrs, ICER is $184,070-213,741 per AIDS case delayed/prevented over 10 years. If analysis includes behaviour change, ZDV versus no treatment is cost-neutral or cost-saving.
Meyer	1994	Includes lost earnings. ZDV versus no treatment is cost-saving.
Double therapy versus monotherapy		
Lacey	1999	Reduced resource use partially (fully in US) offsets drug costs. ICER per progression avoided in 1 year £12,030 (£6,752-21,888), similar in DM and C$ but cost-saving in US due to higher costs of inpatient care.
Simpson	1994	ZDV+Zalc vs ZDV for AIDS patients with CD4 <300 is cost-effective (ECU 12,188-20,708 per life year gained)
Chancellor	1997	Baseline ICER (2 years therapy) £6276. Sensitivity analysis produces ICER £5,976-12,300. Most sensitive to RR
Mauskopf	1998	Baseline ICER $12,603 per life year gained or $18,006 per QALY. Sensitivity analysis produces ICUR $10,608-36,743
Holtgrave	1997	ICUR for double therapy vs monotherapy $50,000-55,000 per QALY gained.
Triple therapy versus double therapy (or monotherapy, or no treatment)		
Brown	1996	Partial evaluation, opportunistic infections (OI) outcomes only. Averted OI costs £5,000 per patient per annum
Messori	1997	ZDV discounted lifetime cost from advanced HIV $93,000 & survival 2.52 years. If additional cost of triple therapy = drug costs ($9500 pa), additional survival will need to be 14 months to have ICER ≤ $30,000
Moore	1996	Over 6 years, 3 year increase in life expectancy triple vs mono therapy. Cumulative cost difference $30,000 thus $10,000 per life year gained. If no offset to healthcare costs, $18,000 per additional life year gained.
Haburchak	1997	Cost per month of life gained $2896-7353 for 6 month gain; $1453-2128 for 3 year gain; ICER $18,000 per life year gained.
Holtgrave	1997	ICUR double vs mono $50k-55k, triple vs double $50k-54k, triple vs mono $50-55k per QALY gained.
Anis	1998	Incremental cost C$283 over one year. Survival benefit 0.027 gives ICER C$10,481 for first year of PI-triple therapy.
Sendi	1999	ICER CHF 33,000 per life year gained (from healthcare perspective). Sensitivity analysis gives ICER <CHF50k. Societal perspective analysis shows HAART versus no treatment is cost-saving.
Cook	1999	Baseline ICER (analysis over a 5 year horizon) is cost-saving, over 20 years ICER is $13,229 per LYG. Sensitivity analysis produces range of ICER $6,683-29,634 and is most sensitive to annual healthcare costs & duration of therapy post-rebound.
Williams	1999	Assumed clinically equivalent. Efa combination has lower annual patient costs due mainly to fewer adverse events

ICER = Incremental cost-effectiveness ratio, i.e. additional cost per additional life year gained
ICUR = Incremental cost-utility ratio, i.e. additional cost per additional quality-adjusted life year gained

Table 19 - Quality Assessment of Economic Evaluations of Antiretroviral Therapy for Persons with HIV Infection

QA against BMJ guidelines:

QA checklist:	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***	***14***	***15***	***16***	***17***	***18***	***19***	***20***	***21***	***22***	***23***	***24***	***25***	***26***	***27***
Studies																											
Scitovsky	✓	✓	×	✓	✓	×	×	✓	✓	n/a	✓	n/a	n/a	n/a	×	✓	✓	✓	n/a	n/a	n/a	✓	✓	n/a	×	✓	×
Moore	✓	✓	×	✓	✓	✓	×	✓	✓	n/a	✓	n/a	n/a	n/a	×	×	✓	✓	✓	n/a	n/a	✓	✓	✓	✓	×	×
Beck	✓	×	×	✓	✓	×	×	✓	✓	n/a	✓	n/a	n/a	n/a	×	✓	✓	✓	✓	n/a	n/a	✓	✓	✓	n/a	✓	×
Lacey	✓	✓	✓	✓	✓	✓	✓	✓	✓	n/a	✓	n/a	n/a	n/a	?	✓	✓	✓	✓	n/a	n/a	✓	n/a	n/a	✓	✓	✓
Brown	✓	✓	×	✓	×	×	×	✓	✓	n/a	✓	n/a	n/a	n/a	×	×	✓	✓	×	n/a	n/a	×	×	n/a	×	×	×
Models																											
Oddone	✓	✓	✓	✓	✓	✓	✓	✓	✓	n/a	✓	n/a	n/a	n/a	✓	✓	✓	✓	n/a	✓	✓	✓	✓	×	n/a	×	✓
Schulman	✓	✓	✓	×	✓	✓	×	✓	✓	n/a	✓	n/a	n/a	n/a	×	✓	✓	✓	✓	✓	×	✓	✓	×	n/a	×	✓
Paltiel	✓	✓	×	✓	✓	✓	×	✓	×	×	✓	n/a	n/a	n/a	✓	✓	✓	×	×	✓	✓	✓	×	×	×	×	✓
Meyer	✓	✓	×	✓	✓	✓	✓	✓	✓	n/a	×	n/a	n/a	×	×	×	✓	✓	✓	✓	×	✓	✓	×	n/a	×	×
Simpson	✓	✓	×	✓	✓	✓	?	✓	✓	n/a	✓	n/a	n/a	n/a	×	×	✓	✓	×	✓	✓	✓	×	n/a	×	×	✓
Messori	✓	×	?	×	✓	✓	×	✓	✓	n/a	✓	n/a	n/a	n/a	×	×	✓	✓	×	✓	×	✓	✓	✓	n/a	×	✓
Chancellor	✓	✓	✓	✓	✓	✓	✓	✓	✓	n/a	✓	n/a	n/a	n/a	✓	×	✓	✓	n/a	✓	?	✓	✓	✓	n/a	×	✓
Mauskopf	✓	✓	×	✓	✓	✓	✓	✓	n/a	×	✓	✓	✓	n/a	×	×	✓	✓	✓	✓	✓	✓	✓	✓	n/a	×	✓
Moore	✓	✓	×	×	✓	✓	×	✓	×	n/a	✓	n/a	n/a	n/a	✓	×	✓	×	×	✓	×	✓	✓	×	×	×	×
Haburchak	✓	✓	×	×	×	✓	×	✓	n/a	×	✓	n/a	n/a	n/a	×	×	✓	×	×	✓	×	×	×	×	×	×	×
Holtgrave	✓	✓	×	✓	✓	✓	✓	✓	n/a	×	✓	✓	✓	n/a	×	×	✓	✓	×	✓	×	✓	✓	✓	n/a	×	×
Anis	✓	✓	✓	✓	✓	×	×	✓	×	n/a	✓	n/a	n/a	n/a	✓	×	✓	✓	×	✓	×	×	×	×	×	✓	✓
Sendi	✓	✓	✓	✓	✓	✓	✓	✓	✓	n/a	✓	n/a	n/a	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	n/a	✓	n/a
Cook	✓	×	×	✓	✓	✓	✓	✓	✓	n/a	✓	n/a	n/a	n/a	×	×	✓	✓	✓	✓	✓	✓	✓	×	n/a	×	✓
Williams	✓	✓	✓	✓	✓	✓	✓	✓	×	n/a	✓	n/a	n/a	n/a	×	×	×	×	×	✓	×	✓	×	n/a	×	×	✓

Table 19 - continued

QA checklist:	*28*	*29*	*30*	*31*	*32*	*33*	*34*	*35*
Studies								
Scitovsky	×	×	✓	✓	✓	✓	✓	✓
Moore	×	×	✓	✓	✓	✓	✓	✓
Beck	×	×	✓	✓	✓	✓	✓	✓
Lacey	?	✓	✓	✓	✓	✓	✓	✓
Brown	×	×	?	✓	✓	✓	✓	×
Models								
Oddone	×	✓	✓	✓	✓	✓	✓	✓
Schulman	×	✓	✓	✓	✓	✓	✓	✓
Paltiel	✓	✓	✓	✓	✓	✓	✓	✓
Meyer	×	×	✓	×	×	✓	✓	✓
Simpson	×	✓	✓	✓	✓	✓	✓	✓
Messori	×	✓	?	✓	✓	✓	✓	✓
Chancellor	✓	✓	✓	✓	✓	✓	✓	✓
Mauskopf	×	✓	✓	✓	✓	✓	✓	✓
Moore	×	×	?	✓	✓	✓	✓	✓
Haburchak	×	×	?	✓	×	✓	×	×
Holtgrave	×	×	✓	✓	✓	✓	✓	✓
Anis	×	×	✓	✓	✓	✓	✓	✓
Sendi	n/a	n/a	✓	✓	✓	✓	✓	✓
Cook	?	✓	✓	✓	?	✓	✓	✓
Williams	×	×	✓	✓	✓	✓	✓	×

*Total score is count of met criteria out of applicable criteria

Table 20 - Key to quality assessment criteria

Criteria	*Description*
1	The research question is stated
2	The economic importance of the research question is stated
3	The viewpoint(s) of the analysis are clearly stated and justified
4	The rationale for choosing the alternative programmes or interventions compared is stated
5	The alternatives being compared are clearly described
6	The form of economic evaluation used is stated
7	The choice of form of economic evaluation is justified in relation to the questions addressed
8	The source(s) of effectiveness estimates used are stated
9	Details of the design and results of effectiveness study are given (if based on a single study)
10	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
11	The primary outcome measure(s) for the economic evaluation are clearly stated
12	Methods to value health states and other benefits are stated
13	Details of the subjects from whom valuations were obtained are given
14	Productivity changes (if included) are reported separately
15	The relevance of productivity changes to the study question is discussed
16	Quantities of resources are reported separately from their unit costs
17	Methods for the estimation of quantities and unit costs are described
18	Currency and price data are recorded
19	Details of currency and price adjustments for inflation or currency conversion are given
20	Details of any model used are given
21	The choice of model used and the key parameters on which it is based are justified
22	Time horizon of costs and benefits is stated
23	The discount rate(s) is stated
24	The choice of rate(s) is justified
25	An explanation is given if costs or benefits are not discounted
26	Details of statistical tests and confidence intervals are given for stochastic data
27	The approach to sensitivity analysis is given
28	The choice of variables for sensitivity analysis is justified
29	The ranges over which the variables are varied are stated
30	Relevant alternatives are compared
31	Incremental analysis is reported
32	Major outcomes are presented in a dissaggregated as well as aggregated form
33	The answer to the study question is given
34	Conclusions follow from the data reported
35	Conclusions are accompanied by the appropriate caveats

12 Conclusions and discussion

12.1 Main findings

There is a large body of trial evidence regarding the effectiveness of antiretroviral therapy for HIV positive patients naïve to prior therapy. The majority of the data refers to the effectiveness of monotherapy versus placebo, or double therapy versus monotherapy. There are also data regarding the effectiveness of triple therapy versus double therapy, although the number of trials is substantially smaller. Information on the effectiveness of quadruple therapy or higher is currently lacking in the published domain; the full reports of only two trials were identified, and neither published standard deviations to allow combination[46; 51]. There is also limited information on the effect of specific combinations of the same number of drugs, although many direct comparisons have not been studied in trials. As the number of drugs increases over time, the potential number of combinations increases, reflected by both the double and triple combination data. This poses problems for investigators; the effect of an extra drug over the established regimen must be quantified, but overall assessment becomes complex when there may also be differences between different combinations of the same number of drugs. Economic evaluations alongside RCTs are rare; most information comes from models based on short term data and projected over the longer term.

The results of our study are presented separately for four different outcomes; CD4 count, viral load, disease progression and drug-related adverse events. Both CD4 count and viral load are used to predict clinical outcome in short-term studies and clinical practice. There is a strong rationale for believing that CD4 count and viral load are useful surrogate outcomes. However, the ability to translate these outcomes into clinical outcome and real health is unclear [160-166]. For the purposes of this study, both the CD4 count and viral load would therefore be expected to show results in a similar direction to the disease progression data.

The inclusion criteria for this study, of naïve patients only, was deliberately chosen in order to minimise the potential heterogeneity in results. It is clear that despite this measure, unexplained heterogeneity still remains; this could still be due to the factors investigated (such as trial duration, specific drugs) but cannot be proven with the techniques available. Publication bias is also another major concern when searching for trial literature, where trials with positive effects are preferentially published. In this review (as in many others), publication bias cannot be excluded.

Zidovudine vs placebo

For the zidovudine monotherapy versus placebo (or no treatment) comparison, the CD4 count data was consistent, with no heterogeneity, and showed an overall significant improvement of 47 cells per μl (95% CI 29, 65) with zidovudine. The viral load data was less convincing; there were only three data points and the results showed some heterogeneity. Nevertheless, the point estimates all favoured zidovudine and the most important study showed that zidovudine significantly reduced viral load by 0.6 log copies per ml compared with placebo. The disease progression data also consistently showed an improvement with zidovudine (in fourteen out of fifteen comparisons), but the results were heterogeneous. Further investigation revealed that the odds of progression (zidovudine over placebo) increased as the length of the trial increased (that is, the effect was less favourable to zidovudine in the long term). At one year, the odds ratio was approximately 0.2 in favour of zidovudine.

Double therapy vs monotherapy

Comparing double therapy against monotherapy, both the CD4 count data and the viral load data showed that the majority of results favoured double therapy over monotherapy. Both sets of results showed heterogeneity, and when explored using meta-regression and sensitivity analysis could not be explained by any of the variables investigated. The disease progression data also showed a result favourable to the double therapy in thirteen of the fourteen comparisons. The combined data showed an overall odds ratio for disease progression of 0.63 (95% CI 0.54, 0.75), favouring the double combination therapy. Again, there was a small amount of heterogeneity. Unlike the monotherapy result, this data was not affected by trial duration. These conclusions are comparable with a previous meta-analysis[35] which showed in favour of either ZDV +Did or Zalc over ZDV in disease progression or death, with relative risks for disease progression of 0.74 (0.64, 0.82) and 0.87 (0.72, 0.98) respectively.

Triple therapy vs double therapy

Investigation of the effect of triple therapy compared with double therapy revealed highly heterogeneous CD4 count and viral load data, although all the results favoured triple therapy. The disease progression data was not statistically heterogeneous and showed that there was no difference between triple therapy and double therapy (odds ratio 0.94 (0.55, 1.59). However, the event rates were small and the confidence intervals wide, therefore, an important overall difference cannot be excluded.

Overall effectiveness data

To summarise the effectiveness data: overall there was a degree of heterogeneity between the results which could not be adequately explained. However, within each set of comparisons, the viral load, CD4 count and disease progression data (with the exception of triple comparisons) confirmed a result in favour of the higher level therapy, suggesting that triple > double > mono > no therapy.

Drug-related adverse events

In terms of the drug-related adverse events, it is clear that zidovudine monotherapy increases the odds of patients dropping out of the trial compared with those on placebo because of intolerance of the side effects of the drug. There appears to be no difference in these severe adverse events between double therapy and monotherapy, but an unclear result between triple therapy and double therapy. It is not clear how representative these trials would be of patients refusing to remain on particular treatment in the clinical setting.

Within levels of therapy (i.e. combinations of the same numbers of drugs), the data were limited to a few particular comparisons with many combinations not tested head-to-head with the triple combinations limited to only two different comparisons. The results were generally inconsistent, and unfortunately do not allow any conclusions regarding the effectiveness of different combinations to be drawn.

Summary

The evidence presented in this report underlines the difficulties of quantifying the effectiveness of different combination antiretroviral therapy. From double therapy onwards, the data on effectiveness has not been fully established, and if trials continue to use a range of different comparators, the effectiveness of many which are not well established themselves, this will lead to difficulties in disentangling the effectiveness of new therapies. A strategy

needs to be taken whereby standard comparators of known efficacy are used, and new combinations are trialled head-to-head with the other combinations of the same number of drugs.

Cost-effectiveness

In terms of the cost-effectiveness, the available studies are difficult to interpret. There were o economic evaluations alongside trials in naïve patients, and the remaining studies were based on a mixture of naïve and experienced patients, and a mixture of trials, observational data and models. The major problem is projecting long term costs and outcomes from short term data. The range of values may be between £4000 and £20,000 per life year saved; but this does not take into account the major productivity losses in a predominantly young, middle-income patient-group.

12.2 What does this mean for clinical practice and public health?

It should be encouraging to patients and clinicians, and reassuring to commissioners that the overall trend suggests that each increase in the number of drugs results in an improvement of clinical status as measured by CD4 count and viral load. This might eventually be confirmed by long-term disease progression, but the results currently available should be interpreted with caution. However, given the nature of the HIV field and the frequent short trials, it is the best information available at the present time. The effects on long-term clinical outcome can only be proven with long-term trials, and this is unlikely to occur in the future as the field moves so rapidly with new drugs and combinations available so quickly. The study here has attempted to confirm and quantify the improvements which have only been suspected in the past with the limited analyses available. The cost-effectiveness information is less clear, and cannot provide accurate results with the data available. In view of the difficulties of the HIV-field, this may never be possible.

Clinicians and policy makers treating and producing HIV guidance should proceed cautiously when contemplating the next addition of drugs. No doubt the pharmaceutical companies will be anxious that four drugs should prove more effective than three, but, given the explosion of costs which would occur, it is essential that this is fully evaluated before implementation. Triallists should be aware of the limitations of short-term trials underpowered for detecting differences in clinical outcome, the problems of over-interpreting positive small trials, and the potential confusion of investigating and comparing different combinations. The rapid development of therapy in stages (mono, double, triple) rather than specific combinations has left a legacy of problems which are not easily resolvable. Ideally, trials should have several arms, with head to head comparisons and combinations with a common basic dual/triple component.

12.3 Limitations of this study

This type of study has several limitations, inherent to both the subject area and information available and also to the approach taken:

1. In order for the data to be combined, a series of assumptions were made (see appendix 13.4). In particular, medians (where given) were assumed to be means (although this is less likely to be a problem for outcomes measuring differences from baseline).

2. To a certain extent, the timepoint for the CD4 and viral load data was forced in order to incorporate the most amount of information but to restrict the dropout rate.
3. Data were frequently missing (particularly standard deviations of the change in CD4 count or viral load), and this was not obtained from the investigators.
4. Disease progression incorporated outdated endpoints in the earlier trials. However, as patients were randomised, the relative differences between arms should remain valid.
5. The relative paucity of data points made meta-regression less powerful.
6. The lack of data from quadruple (or higher) combinations meant that future predictions of the effect of additional drugs was impossible.
7. It is important to examine baseline status as a possible confounding factor – but this is limited with the techniques used.
8. Conference data which might give further information were exceedingly sparse in detail and could not be used.
9. It may be that it is inappropriate to look at different drugs (within each category) together.
10. This study only looks at one aspect of HIV treatment – the effectiveness in naïve patients.

12.4 Further research

More information is required on the effectiveness in naïve patients of triple drug therapies overall, and also particular combinations. The effect of higher combinations must be researched and fully reported before implementation. Head to head trials would help to clarify the effects of individual drugs and combinations and to untangle whether the number of drugs or the specific drug combinations are more important. Larger trials with adequate power, and with factorial designs are needed. In terms of overall effectiveness, meta-analysis using individual patient data (IPD) would help to overcome problems with missing data, make the results more accurate and allow more complex survival analysis. IPD meta-analyses are more powerful, and allow better exploration of heterogeneity. In view of the short term nature of trials, good quality cohort studies might provide better estimates of lifetime costs and outcomes.

13 Appendices

13.1 Tables 7a-7d Study Characteristics

Table 7a Study Characteristics: monotherapy versus anything

Trial identifier	*Paper*	*Type of study report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
Fischl	ID:333 Fischl, 1987[61]	Main analysis	Age criteria NS. AIDS (with PCP) or ARC. CD4 <500	NS	282 (269/13) Mean age NS Mean CD4 = NS ARC = 43% AIDS = 57%	1.ZDV (1500mg) 2.P	145 137	Death Disease progression CD4 count Karnofsky score Weight	NS	Designed for 24 wks. 27 completed 24 wks. Mean 17 wks.
	ID:339 Richman, 1987[60]	Adverse events only	NS	NS	282 (NS) No other details	1.ZDV (1500mg) 2.P	145 137	Adverse events	NS	NS
	ID:415 Day, 1992[95]	Subgroup	Age criteria NS. AIDS (with PCP) or ARC. NOT dementia.	NS	32 (29/3) Mean age 36 ARC = 59% AIDS = 41%	1.ZDV (NS) 2.P	Total = 32	Dementia (DSM-III)	NS	2 years
	ID:120 Parks, 1988[96]	Subgroup Single centre	NS	NS	38 (NS) No details	1.ZDV (NS) 2.P	Total = 38	Time to pos virus isolation	NS	NS
	ID:119 Spector, 1989[97]	Subgroup	Age ≥ 18 AIDS or ARC CD4 <500	NS	29 (NS) Mean age 35 ARC = 52% AIDS = 48%	1.ZDV (1500mg) 2.P	16 13	Serum p24	NS	20 weeks trt
	ID:402 Wu, 1990[98]	Subgroup	Age criteria NS AIDS or severe ARC	NS	32 (28/4) Mean age 36 Mean CD4 = 152 ARC = 56% AIDS = 44%	1.ZDV (1500mg) 2.P	16 16	Death QOL	NS	Mean 19 weeks on blinded trt
	ID:122 Chaisson, 1988[99]	Subgroup	Age NS AIDS or ARC	NS	158 (NS) Age NS	1.ZDV 2.P	83 75	Disease progression CD4 count HIV core Ag	NS	Median 16 weeks on trt
Lane	ID:265 Lane, 1989[79]	Main analysis	Age 18-60 AIDS & KS & CD4>200 No opp. infections	NS	37 (37/0) Mean age 39 Mean CD4 = 539	1.ZDV 15mg/kg iv 2.ZDV 3mg/kg iv 3.ZDV (1500mg) oral 4.P	10 9 9 9	Disease progression CD4 count CD8 count Adverse events Hb levels Granulocyte counts Platelet counts CSF HIV culture CSF ZDV levels HIV antigen	NS	12 weeks
	ID:408 Walker, 1988[100]	Preliminary safety results	Age criteria NS. AIDS & KS & CD4 >200 No opp. infections	NS	20 (20/0) Age 18-60 No details	1.ZDV 15mg/kg iv 2.ZDV 3mg/kg iv 3.ZDV (1500mg) po 4.P	5 5 5 5	Preliminary serum erythropoietin	NS	12 weeks

Trial identifier	*Paper*	*Type of study report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
ACTG 019	ID:113 Volberding, 1990[77]	Main analysis Patients with CD4 < 500	Age >18 CD4 <500; not AIDS or ARC	NS?	1338 (1231/107) 84% age 25-45	1.ZDV (1500mg) 2.ZDV (500mg) 3.P	457 453 428	Death Disease progression CD4 count Serum p24 Adverse events	AIDS; advanced ARC; severe or recurrent side effects.	Mean follow up = 55,61,52 weeks Mean trt = 43, 50, 52 weeks.
	ID:152 Volberding, 1995[76]	Main analysis Patients with CD4 ≥ 500	Age criteria NS CD4 ≥ 500 (see ID: 113)	NS?	1637 (NS). 1609 started trt. Median age 33 Median CD4 = 655	1.ZDV (1500mg) 2.ZDV (500mg) 3.ZDV deferred (500mg)	541 549 547	CD4 count Disease progression Death Adverse events	Open label ZDV offered when CD4 <500	Follow up = 4.8 yrs Median blinded trt = 1.6yrs.
	ID:187 Koch, 1992[101]	Adverse events only	Age ≤ 18 CD4 ≤ 500 Asymptomatic	NS	1567 (1426/141) Mean age NS	1.ZDV (1500mg) 2.ZDV (500mg) 3.P	529 544 494	Adverse events & toxicity	AIDS; advanced ARC; severe or recurrent side effects; prolonged non-compliance	Mean 48, 46, 41 weeks
	ID:88 Lenderking, 1994[102]	Duplicate publication	Age criteria NS Asymptomatic	NS	1338 (NS) Mean age NS	1.ZDV (1500mg) 2.ZDV (500mg) 3.P	457 453 428	Disease progression Death Adverse events	NS	Mean follow up = 55,61,52 weeks
ACTG 016	ID:112 Fischl, 1990[78]	Main analysis	Age criteria NS CD4 200-800; mildly symptomatic	NS?	711 (672/38) Mean age 35 Mean CD4 = 425	1.P 2.ZDV (1200mg)	351 360	Death Disease progression Adverse events CD4 count HIV Antigen	Life-threatening toxicity; AIDS-defining condition or advanced ARC; non-compliance.	Intended 104 weeks. Median 11mths. 68% completed 24 weeks. Mean duration trt = 9mths.
	ID:100 Wu, 1993[103]	Subgroup	Age criteria NS. Men only. CD4 200-800 Early symptomatic disease	NS	70 (70/0) Mean age 35 Mean CD4 = 413	1.ZDV (1200mg) 2.P	36 34	QOL	NS	Up to 24 weeks.
	ID:101 Bass, 1992[104]	Subgroup	Age criteria NS CD4 200-500 & mildly symptomatic	NS	61 (NS)	1.ZDV (1200mg) 2.P	34 27	CD4 count Serum neopterin Serum β2M	NS	All observed for 24 weeks; 72% for 39 weeks
	ID:105 Gelber, 1992[105]	Subgroup	NS	NS	711 (NS)	1.ZDV (1200mg) 2.P	360 351	Adverse events Time to event (adverse effects/disease prog)	NS	Median 11mths.
Gill	ID:106 Gill, 1991[65]		Adults? Asymptomatic or PGL Serum p24 Ag pos	None in the last 6 mths	34 (33/1) Mean age 33 Mean CD4 = 470	1.ZDV (600mg – 400mg x 2) 2. ZDV (300mg – 200mg x 4) 3. P	11 11 12	CD4 count Serum p24 Adverse events	NS	6 wks – 12 wks

Trial identifier	*Paper*	*Type of study report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
NHF-ACTG 036	ID:160 Merigan, 1991[74]		Haemophiliac Age ≥ 12 CD4 ≤ 500 Asymptomatic	NS	193? (NS) Median age 31 Median CD4 = 283	1.ZDV (1500mg) 2.P	92? 101?	Disease progression Death CD4 count Adverse events Weight change	NS	Average 9.6 mths on study.
VACS 298	ID:104 Hamilton, 1992[64]	Main analysis	Age criteria NS Symptoms but not AIDS CD4 200-500	NS	338 (335/3) Mean age 40 Mean CD4 = 355	1.ZDV (1500mg) 2.P then deferred ZDV when CD4 <200	170 168	Death Disease progression CD4 count Adverse events Serum p24	When CD4 <200	Mean 28 months; 14.8mths, 13.9mths on blinded therapy
	ID:400 O'Brien, 1996[63]	Subgroup	Age criteria NS Symptomatic CD4 200-500	NS	270 (NS) Age NS No details	1.ZDV immediate (1500mg) 2.ZDV deferred	129 141	Plasma viral load CD4 count Serum β2M Disease progression	When CD4 <200 or AIDS defining disease	1 year?
EACGS	ID:179 Cooper, 1993[69]	Main analysis	Age ≥ 18 Asymptomatic or PGL CD4 >400	NS	984 (841/143) Mean age 31 Mean CD4 = 650 CDC II = 56%	1.ZDV (1000mg) 2.P	495 489	Disease progression CD4 count Adverse events Serum p24 Compliance	NS	Median trt 93, 94 wks
Davey	ID:394 Davey, 1993[71]		Age criteria NS. Asymptomatic or KS; CD4 ≥ 200 Pos plasma virus culture	AZT ≤ 6 mths. 31% prior AZT	84 (78/6) Mean age 35 Mean CD4 = 588 Asymptomatic = 100%	1.Placebo 2.L-697,661 (50mg) 3. L-697,661 (300mg) 4. L-697,661 (1000mg) 5.ZDV (500mg)	17 17 17 17 16	Disease progression Plasma viral load % CD4 Serum β_2M Serum p24 Plasma drug conc. Resistance	AIDS defining illness	69% completed 12 weeks trt
Koot, 1993	ID:177 Koot, 1993[73]		Age criteria NS CD4 200-400 or HIV-1 antigenaemia; CDC II or III	NS?	52 (52/0) Mean age 36 Median CD4 = 350, 330	1.ZDV (1000mg) 2.P	29 23	Disease progression CD4 count CD3 count	NS	Intended max 25 mths. Median 18-20 mths?
Concorde	ID:87 Anon, 1994[62]	Main analysis	Age >13 asymptomatic	None within 3 mths	1749 (1478/271) Mean age 32 Mean CD4 = NS 70% had CD4 > 350	1. Immediate ZDV (1000mg) 2. P; then deferred ZDV until AIDS or ARC symptoms or CD4 <500	877 872	Death Disease progression Adverse events CD4 count	NS	Median 3.3 yrs?
	ID:22 White, 1997[106]	"On-treatment" analysis	NS	NS		1.Immediate ZDV (1000mg) 2.Delayed ZDV (1000mg)				

Trial identifier	*Paper*	*Type of study report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
	ID:63 Baldeweg, 1995[107]	Subgroup London Centres Neuropsychol-ogical evaluation	NS	NS	27 (27/0) Mean age 37	1.ZDV (1000mg) 2.P	16 11	Neuropsychological assessment Disease progression CD4 count CD8 count Serum β_2M	NS	All 28 months
	ID:169 Gruzelier, 1996[108]	Subgroup Neuropsychol-ogical evaluation	Asymptomatic	NS	27 (27/0) Mean age 37	1.ZDV (1000mg) 2.P	16 11	Neuropsychological assessment	NS	All 28 months
Mannucci, 1994	ID:82 Mannucci, 1994[66]		Age ≥ 13 yrs Asymptomatic or PGL CD4 100-400 P24 measurable	NS	140 (138/2) Median age 27, 28 Median CD4 = 279, 277 CDC II = 74% CDC III = 26%	1.ZDV (1000mg) 2.P	69 71	Death Disease progression CD4 count* Adverse events Serum p24	NS	Median time on study Pl = 80 wks ZDV= 99 wks
EACG 017	ID:81 Mulder, 1994[67]		Age ≥ 18 CD4 200-400 or if >400, p24+.	No	329 (303/26) Age NS Median CD4 = 313, 320 CDC II = 59% CDC III = 41%	1.ZDV (1000mg) 2.P	167 162	Death Disease progression CD4 count* Adverse events Compliance Serum p24	NS	Median ZDV=60 wks P= 57wks
Kinloch-de-Loes, 1995	ID:156 Kinloch-de-Loes, 1995[68]		Primary HIV infection Age ≥ 18 P24 Ag+	NS	77 (68/9) Mean age 31 Mean CD4 = 497 Mean VL = 7.35 (n=53)	1.ZDV (500mg) 2.P	39 38	Death Disease progression CD4 count Plasma viral load Adverse events CD8 count Serum p24 Duration of acute retroviral syndrome	NS	82% completed trt for 6 mths
ACTG 116A	ID:76 Dolin, 1995[48]		Age NS AIDS or ARC with CD4 ≤ 300 or asymptomatic with CD4 ≤200	ZDV ≤16 wks 38% had prior ZDV.	617 (593/24) Median age 35 Mean CD4 = 130 Asymptomatic = 7% ARC = 67% AIDS = 26%	1.ZDV (1200mg then 600mg) 2.Did (500mg) 3.Did (750 mg)	212 197 208	Death Disease progression CD4 count* Serum p24	NS	Median time initial therapy 60 weeks. Median follow-up 85 wks.
ACTG 114	ID:78 Bozette, 1995[75]	Subgroup	Age criteria NS CD4 <200 & either history of PCP or other symptoms	16% had prior ZDV	338 (319/9) Mean age 37 Mean CD4 = 95 AIDS = 29%	1.Zalc (2.25mg) 2.ZDV (600mg)	174 164	QOL	NS	Median 48, 54 wks

Trial identifier	*Paper*	*Type of study report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
Nordic	ID:129 Nielsen, 1996[72]		Age criteria NS AIDS or ARC	No	46 (NS) Mean CD4 = 132	1.ZDV (600mg) 2.Did (400mg or 500mg sachet) 3.Monthly alternating ZDV/Did	18 13 15	Resistance	NS	≥12 mths Mean 18.9 mths
ISS 902	ID:24 Floridia, 1997[57]		Age >16 ARC	No	554 (396/158) Mean age 32 Mean CD4 = 242 Advanced ARC = 22%	1.ZDV (1000mg) 2.Did (750mg sachet)	275 279	Death Disease progression CD4 count Adverse events Serum p24 Body weight	NS	Mean trt 13.5 mths Median follow-up 20 mths
DATRI 002	ID:225 Niu, 1998[70]		Age ≥13 P24+ or seroconversion within 30 days Primary HIV infection	None	28 (24/4) Mean age NS Median CD4 = 584 Median VL = 5.68	1.ZDV (1000mg) 2.P	13 15	CD4 count Plasma viral load Cellular viral load Serum neopterin	NS	24 weeks on trt
Evers	ID:246 Evers, 1998[56]		All stages but NOT lymphoma or opp infections of CNS	NS	98 (86/12) Mean age 37 Mean CD4 = 264 CDC 1 = 17% CDC 2 = 47% CDC 3 = 36%	1.ZDV (500mg) 2.Untreated	47 51	CD4 count Serum p24 Serum β2M Neurological studies eg. ERP, EEG	NS	Mean 1.2 yrs

Table 7b Study Characteristics: double versus anything

Trial identifier	*Paper*	*Type of report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention (dose per day)*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
Kaulen	ID:195 Kaulen, 1993[83]	Main analysis	Age criteria NS CD4 < 500 Advanced HIV	No	85 (NS) Age NS Mean CD4 = 213 Stage ≤ III = 61% Stage IV = 39%	1.ZDV (500mg/kg) 2.ZDV (500mg/kg) + Zalc (0.02mg/kg)	42 43	CD4 count CD8 count Retinal infections	NS	36 wks
Yarchoan	ID:91 Yarchoan, 1994[53]	Main analysis	Age ≥18 AIDS or symptomatic HIV; CD4 10-350	< 3mths	41 (37/4) Age 18-53 Median CD4 = 183, 202 AIDS = 29%	1.ZDV (300mg) + Did (250mg sachet) 2.ZDV (600mg) alternating with Did (500mg sachet) (every 3 wks)	21 20	Death Disease progression CD4 count Adverse events Serum β_2M Serum p24 Body weight	NS	Follow-up range 33-104 wks
	ID:19 Brouwers, 1997[109]	Subgroup	Age criteria NS. AIDS or symptomatic HIV; CD4 10-350 Ambulatory and free from active life-threatening infections. Patients with possible CNS compromise.	< 3mths	34 (31/3) Mean age 34. Mean CD4 = 183	1.ZDV (300mg) + Did (250mg sachet) 2.ZDV (600mg) alternating with Did (500mg sachet) (every 3 wks)	>20 >14	Neurophysiological assessment	NS	Intended 12 weeks. 88% had complete follow-up.
Kojima	ID:73 Kojima, 1995[110]	Subgroup (first 26 who completed 45 wks trt)	Age criteria NS AIDS or symptomatic HIV	<6 mths 35% had prior trt	26 (23/3) Median age 32,34 Mean CD4 = 175 ARC = 81% AIDS = 19%	1.ZDV (300mg) + Did (250mg sachet) 2.ZDV (600mg) alternating with Did (500mg sachet) (every 3 wks)	Total = 26	CD4 count Plasma VL Resistance	NS	All complete 45 wks therap
NUCA 3001	ID:146 Eron, 1995[81]	Main analysis	Age ≥ 12 CD4 200-500	ZDV ≤ 4 wks Median ≤ 3 wks	366 (320/44) Median age 34 Mean CD4 = 359 Mean VL = 4.92 Asymptomatic = 73%	1.ZDV (600mg) 2. Lam (600mg) 3. ZDV (600mg) + Lam (300mg) 4. ZDV (600mg) + Lam (600mg)	93 87 92 94	CD4 count Plasma viral load Serum p24 Serum β_2M Serum neopterin Adverse events Dis prog	NS	At 24 wks, 75 still receiving study drug. 4 55% left at week 52.
	ID:34 Eron, 1996[111]	Duplicate publication	Age ≥ 12 CD4 200-500 No active opp. Infections 81% asymptomatic	< 4wks ZDV	366 (318/48) Mean age 35 Mean CD4 = 359 Asymptomatic = 81% CDC B = 18% CDC C = 2%	1.ZDV (600mg) 2. Lam (600mg) 3. ZDV (600mg) + Lam (300mg) 4. ZDV (600mg) + Lam (600mg)	Total = 366	CD4 count Plasma viral load Serum p24 Adverse events % CD4	NS	75% complet 24 weeks. 60% complet 52 weeks.

Trial identifier	*Paper*	*Type of report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention (dose per day)*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
	ID:44 Kuritzkes, 1996[112]	Subgroup	Adults? Median age 31-34 No other details	No	N varied. Median age 34 Median VL = 4.6	1.ZDV (600mg) 2. Lam (600mg) 3. ZDV (600mg) + Lam (300mg) 4. ZDV (600mg) + Lam (600mg)	Varied by assay	Plasma viral load Resistance Syncytium formation	NS	24 wks plann
Vella	ID:207 Vella, 1996[80]	Main analysis	Age 18-65 Symptomatic CD4 ≤ 300	No	92 (62/30) Mean age 33 Mean CD4 = 177? CDC III = 45% CDC IV = 55%	1.Saq (1800mg) 2.ZDV (600mg) 3.Saq (225mg) + ZDV (600mg) 4.Saq (600mg) + ZDV (600mg) 5.Saq (1500mg) + ZDV (600mg)	19 17 18 18 20	CD4 count Plasma viral load Deaths Adverse events* Disease progression Pharmacokinetics Serum β_2M Serum neopterin Serum p24 Plasma infectivity	NS	16 weeks
	ID:371 Andreoni, 1998[113]	Subgroup. Patients with >1yr trt.	Age NS Symptomatic CD4 ≤ 300	No	44 (NS) Age NS Mean CD4 = 178 Mean VL = 5.7	1.ZDV (600mg) 2.Saq (1800mg) 3.ZDV (600mg) + saq (1800mg)	14 13 17	Resistance		> 1yr
	ID:170 Sarmati, 1997[114]		Age NS Symptomatic CD4 ≤ 300	No	33 (NS) Age NS Mean CD4 = 160 Mean VL = 5.37	1.ZDV (600mg) 2.Saq (1800mg) 3.ZDV (600mg) + saq (1800mg)	11 11 11	Plasma viral load CD4 count Neutralising Ab titre	NS	16 weeks
	ID:322 Vella, 1996[115]		Age NS CD4 < 300	No	92 (NS) Age NS Median CD4 = 156-248 Median VL = 5.2-5.3	1.Saq (1800mg) 2.ZDV (600mg) 3.Saq (225mg) + ZDV (600mg) 4.Saq (600mg) + ZDV (600mg) 5.Saq (1500mg) + ZDV (600mg)	Total =92	CD4 count Plasma viral load	NS	24 weeks
ACTG 175	ID:153 Hammer, 1996[47]	Naïve stratum	Age ≥ 12 CD4 200-500 No AIDS-defining illness (except minimal KS)	No	1067 (892/175) Mean age 34 Mean CD4 = 372	1.ZDV (600mg) 2.ZDV (600mg) + Zalc (2.25mg) 3.ZDV (600mg) + Did (400mg) 4. Did (400mg)	269 263 267 268	Disease progression Death CD4 count Adverse events	NS	Median 135 weeks. 25% loss to follow up. Median 106 weeks trt.
	ID:370 Kastrissios, 1998[116]	Subgroup	Age criteria NS. CD4 200-500.	NS	722 (NS) Median age 35.	1.ZDV (600mg) 2.Did (400mg) 3.ZDV (600mg) + Zalc (2.25mg) 4.ZDV (600mg) + Did (400mg)	167 192 152 181 (no. analysed)	Adherence	If endpoint achieved.	NS
	ID:363 Simpson, 1998[117]	Subgroup - neuropathy	Age criteria NS. CD4 200-500	No	1067? (NS) Median age 35.	1.ZDV (600mg) 2.Did (400mg) 3.ZDV (600mg) + Zalc (2.25mg) 4.ZDV (600mg) + Did (400mg)				NS

Trial identifier	*Paper*	*Type of report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention (dose per day)*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
DELTA-1	ID:52 Anon, 1996[50]	Main analysis	Age ≥ 15 Symptoms or CD4 < 350	No	2124 (1773/351) Mean age 36 Mean CD4 = 214 Asymptomatic = 58% Symptomatic = 30% AIDS = 12%	1.ZDV (600mg) 2. ZDV (600mg) + Did (400mg) 3. ZDV (600mg) + Zalc (2.25mg)	700 718 706	Death Disease progression CD4 count Adverse events	Disease progression or CD4 ≥ 59% decrease (or later if >2yrs blinded treatment)	5083 person years. Mean 2.4 yea
	ID:364 Anon, 1999[49]	Subgroup (extended virology study)	Age criteria NS AIDS with CD4 <50 or ARC or asymptomatic CD4<350	No	748 (NS) Mean age 36 Mean CD4 = 215 Mean VL = 4.7 Asymptomatic = 48%? ARC = 36% AIDS = 16%	1.ZDV (600mg) 2. ZDV (600mg) + Did (400mg) 3. ZDV (600mg) + Zalc (2.25mg)	298 304 311	Viral load		Median 31 months?
	ID:171 Brun-Vezinet, 1996[118]	Subgroup	Age criteria NS AIDS with CD4 > 50 or asymptomatic with CD4 <350	No	240 (NS) Age NS Mean CD4 = 207 Median VL = 4.71 Asymptomatic = 53% Symptomatic = 30% AIDS = 17%	1.ZDV (600mg) 2. ZDV (600mg) + Did (400mg) 3. ZDV (600mg) + Zalc (2.25mg)	87 80 73	CD4 count Plasma viral load Serum p24 Resistance Cellular viral load Syncytium-inducing strains	NS	Median duration of tr 21mths 17mths 23mths
	ID:221 Bruisten, 1998[119]	Subgroup	Criteria NS > 80 weeks follow-up.	NS	42 (NS) Age NS Median CD4 = 185, 180, 270 Median VL = 5.09, 4.99, 4.73	1.ZDV (600mg) 2. ZDV (600mg) + Did (400mg) 3. ZDV (600mg) + Zalc (2.25mg)	17 12 13	CD4 count Plasma viral load Cellular viral load	NS	>80wks
NUCB 3001	ID:48 Katlama, 1996[82]	Main analysis	Age ≥ 18 CD4 100-400	≤ 4 wks	129 (95/34) Mean age 35 Mean CD4 = 270 Mean VL = 5.22 Asymptomatic = 64% CDC B = 26% CDC C = 9%	1.ZDV (600mg) 2. ZDV (600mg) + Lam (600mg)	65 64	CD4 count Serum β_2M Serum neopterin Serum p24 Plasma viral load Adverse events Disease progression	NS	88% complet 24 weeks
	ID:34 Eron, 1996[111]	Duplicate publication	Age ≥ 18 CD4 100-400 No opportunistic infections.	< 4 wks ZDV	129 (94/35) Mean age 35 Mean CD4 = 271 Asymptomatic = 64% CDC B = 26% CDC C = 9%	1.ZDV (600mg) 2. ZDV (600mg) + Lam (600mg)	Total n = 129	CD4 count Plasma viral load Serum p24 Adverse events % CD4	NS	88% complet 24 weeks
	ID:139 Larder, 1995[120]	Substudy	NS	No	50 (NS) Mean VL = 5.14	1.ZDV (600mg) 2. ZDV (600mg) + Lam (600mg)	Total n=50	Plasma viral load Resistance	NS	90% complet 24 weeks

Trial identifier	*Paper*	*Type of report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention (dose per day)*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
Protocol 34,225-02	ID:54 Schooley, 1996[84]	Main analysis	Age NS CD4<300	≤4 wks	180 (162/18) Mean age 36 Mean CD4 = 143 Mean VL = 5.0	1. ZDV (600mg) 2. ZDV (600mg) + Did (200mg) 3. ZDV (600mg) + Zalc (2.25mg)	60 59 61	Death Disease progression CD4 count Plasma viral load Adverse events	NS	52 weeks
	ID:131 Larder, 1996[121]	Resistance	Age criteria NS CD4<300	<4 wks ZDV (& no other)	No details	1.ZDV (600mg) + Did (200mg) 2.ZDV (600mg) 3.ZDV (600mg) + Zalc (2.25mg)	NS	Resistance	NS	48 wks
M50003	ID:259 Moyle, 1997[86]	Main analysis	Adults CD4 300-500 & no prior AIDS-defining illness	Max 20% prior trt	256 (181/75) Mean age 33 Median CD4 = 410, 399 CDC I = 2% CDC II = 77% CDC III = 10% CDC IV = 11%	1.ZDV (500-600mg) 2.ZDV (500-600mg) + Zalc (2.25mg)	127 129	CD4 count Disease progression Death Adverse events QOL	After 12 wks, if CD4 <300, ZDV offered comb and ZDV/Zalc offered other at clinician's discretion	Intended 104 wks. 41% completed 10 wks follow u 32% on blind therapy. Median follo up = 91wks Median blind trt = 71 wks
NAT002	ID:496 Fisher, 1998[87]	Main analysis	Age > 18 CD4 150-350 & no more than 2 HIV-1 unrelated illnesses	No	78 (39/39) Mean age 31 Mean CD4 = 255 Mean VL = 4.26	1.Did (400mg) 2.Stav (40mg) + Did (200mg) 3.Stav (40mg) + Did (400mg) 4.Stav (80mg) + Did (200mg) 5.Stav (80mg) + Did (400mg	15 16 16 15 16	CD4 count Plasma VL Adverse events	NS	24 weeks
Foudraine	ID:222 Foudraine, 1998[54]	Main analysis	Age criteria NS CD4 ≥ 200 VL ≥ 10,000	No	47 (NS) Median age 38. Median CD4 = 315, 290 Median VL = 4.8, 4.98	1.ZDV (600mg) + Lam (300mg) 2.Stav (80mg) + Lam (300mg)	24 23	CD4 count Plasma viral load Adverse events Resistance	NS	12 weeks
	ID:236 Foudraine, 1998[122]	Substudy	Age criteria NS Not AIDS CD4 ≥ 200 Viral load ≥ 10,000	No	28 (NS) Median age 39, 36 Median CD4 = 330, 290 Median VL = 4.81, 4.98	1.Lam (300mg) + Stav (80mg) 2.Lam (300mg) + ZDV (600mg)	17 11	CSF HIV RNA CSF p24 CSF cell count CSF drug conc Plasma drug conc	NS	12 weeks

Trial identifier	*Paper*	*Type of report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention (dose per day)*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
A1455-053	ID:496 Fisher, 1998[87]	Main analysis	NS	No	137 (97/40) Median age 33 Median CD4 = 316 Median VL = 4.7 Not-AIDS = 88% AIDS = 12%	1.ZDV (600mg) + Did (standard) 2.Stav (standard) + Did (standard)	70 67	CD4 count Plasma VL Adverse events	NS	36 weeks
	ID:256 Angarano, 1997[123]	(Ongoing study)	Age criteria NS CD5 ≤ 500	No	125 (88/37) Mean age 35	1.Stav (50mg) + Did (400mg) 2.ZDV (400mg?) + Did (600mg?)	NS	None yet	NS	Ongoing?
Izopet, 1999	ID:427 Izopet, 1999[85]	Main analysis	Age criteria NS Asymptomatic CD4 250-500	No	54 (NS) Mean age 37 Mean CD4 = 372 Mean VL = 4.28	1.ZDV (500mg) + Zalc (2.25mg) intermittent, 6 wk cycle on/off 2.ZDV (500mg) + Zalc (2.25mg) continuous	27 22 (analysed)	CD4 count Plasma VL Cellular VL Resistance Adverse events	Intolerance; CD4 <200?	61% complet 54 weeks.
ACTG 306	ID:430 Kuritzkes, 1999[59]		Age ≥ 12 CD4 200-600	< 7 days nucleoside analogue	292 (248/44) Median age 33-36 Median CD4 = 391 - 407 Median VL = 4.05 - 4.06	1.Stav (80mg) + Lam (300mg) 2.ZDV (600mg) + Lam (300mg) 3.Stav (80mg) 4.Did (400mg) + Lam (300mg) 5.ZDV (600mg) + Lam (300mg) 6. Did (400mg)	54 57 35 54 55 37	CD4 count Plasma VL Adverse events Disease progression?	Serious adverse events	93% still on study trt at week 24
	ID:496 Fisher, 1998[87]		Age ≥ 12 CD4 200-600	None	299 Median age 33 (Did arm), 36 (Stav arm) Median VL= 11,147, 10,146 Median CD4 =391, 407	1.Stav (80mg) + Lam (300mg) 2.ZDV (600mg) + Lam (300mg) 3.Stav (80mg) 4.Did (400mg) + Lam (300mg) 5.ZDV (600mg) + Lam (300mg) 6. Did (400mg)	54 57 35 54 55 37	CD4 count Plasma VL	NS	24 weeks
ALBI	ID:431 Molina, 1999[55]	Main analysis	Age >18 CD4 ≥ 200 Plasma VL 10,000-100,000	No	151 (131/20) Mean age 36 Mean CD4 = 404 Mean VL = 4.54 AIDS = 3%	1.ZDV (500mg) + Lam (300mg) 2.Stav (80mg) + Did (400mg) 3.Stav (80mg) + Did (400mg) alternating with ZDV (500mg) + Lam (300mg) 12 wks each	51 51 49	CD4 count Plasma VL Disease progression Death Adverse events	Toxicity; disease prog; CD4 below baseline; <50% VL reduction after 12 weeks	90% remaine on trt at 24 weeks
	ID:507 Molina, 1999b[124]	Duplicate publication	CD4 ≥ 200 Plasma VL 10,000-100,000	No	151 Mean age 36 Mean CD4 = 404 Mean VL = 4.54	1.ZDV (500mg) + Lam (300mg) 2.Stav (80mg) + Did (400mg) 3.Stav (80mg) + Did (400mg) alternating with ZDV (500mg) + Lam (300mg) 12 wks each	51 51 49	CD4 count Plasma VL Adverse events	NS	90% remaine on trt at 24 weeks

Table 7c Study Characteristics: triple versus anything

Trial identifier	*Study*	*Type of report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention (dose per day)*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
INCAS	ID:3 Montaner, 1998[90]	Main analysis	Age ≥ 18 CD4 200-600	None	151 (140/11). Mean age 37. Mean CD4 = 375 Mean VL = 4.4 CDC I = 97% CDC II = 3%	1.ZDV (600mg) + Nev* (400mg) 2.ZDV (600mg) + Did (400mg) 3.ZDV (600mg) + Did (400mg) + Nev* (400mg)	47 53 51	Death Disease progression CD4 count Plasma viral load Adverse events Resistance Other	NS	52 weeks planned. 66% completed this.
	ID:217 Raboud, 1998[125]	Plasma viral load	Age NS Not AIDS CD4 200-500	None	151. No other details.	1.ZDV (600mg) + Nev* (400mg) 2.ZDV (600mg) + Did (400mg) 3.ZDV (600mg) + Did (400mg) + Nev* (400mg)	47 53 51	Plasma viral load	NS	Median 54 weeks
Floridia	ID:372 Floridia, 1999[88]	Main analysis	Age >18 AIDS or CD4<200	No	68 (58/10). Mean age 37. Mean CD4 = 83 Mean VL = 5.6 Asymptomatic = 32% Symptomatic = 28% AIDS = 40%	1.ZDV (600mg)+Did (400mg)+Nev* (400mg) 2.ZDV (600mg) + Did (400mg)	32 36	CD4 count Plasma viral load Disease progression Death Adverse effects Adherence	Severe toxicity; severe rash or cutaneous reaction; pancreatitis; pregnancy; disallowed medications; chemotherapy; radiotherapy	Mean 39 weeks. (48 weeks planned)
ACTG 261	ID:414 Friedland, 1999[89]	Main analysis	Age criteria NS. CD4 100-500	None or < 6mths ZDV or Did. 37% had prior trt, median 2 mths.	544 (445/99). Median age 35. Median CD4 = 295 Median VL = 4.45	1.ZDV (600mg)+Did (400mg)+Del* (1200mg) 2.ZDV (600mg) + Del* (1200mg) 3.Did (400mg) + Del* (1200mg) 4.ZDV (600mg) + Did (400mg)	137 135 135 137	CD4 count Plasma viral load Disease progression Adverse events	NS	48 weeks planned. 64% completed this on protocol therapy.
PISCES	ID:429 Revicki, 1999[58]	Main analysis	Age ≥ 18 CD4 50 - 350 and advanced HIV	ZDV < 16 wks	993 (826/167) Mean age 36.5 Mean CD4 = 200 Mean VL = 4.9	1.ZDV (600mg) + Zalc (2.25mg) 2.ZDV (600mg) + Saq (1800mg) 3. ZDV (600mg) + Zalc (2.25mg) + Saq (1800mg)	327 324 342	QOL	AIDS-related events; toxicity; patient/investigator preference	Median blinded trt = 59.7, 58.4, 63.3 wks
AVANTI-1	ID:499 Gatell, 1999[91]	Main analysis	Age ≥ 18 CD4 150-500; no active AIDS-defining infections or history of lymphoma or KS	None	106 (85/21) Mean age 38	1.ZDV (600mg) + Lam (600mg) 2.ZDV (600mg) + Lam (600mg) + Lov (300mg)	52 54	CD4 count Plasma viral load Disease progression Death QOL	Recurrent grade 3 toxicity	83% completed 52 weeks.
Study 006	ID:500	Main	Age >13	Yes, previous	450 (386/64)	1.Ind (2400mg) + ZDV (600mg) + Lam	148	CD4 count	NS	Intended 48

Trial identifier	*Study*	*Type of report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention (dose per day)*	*n*	*Outcomes*	*Stop criteria*	*Follow-up*
	Staszewski, 1999[92]	analysis	CD4 >50; VL >10,000	NRTI in 15%.	Mean age 36 Mean CD4 =345 Mean VL = 4.77	(300mg) 2.Efa (600mg) + ZDV (600mg) + Lam (300mg) 3. Efa (600mg) + Ind (3000mg)	 154 148	Plasma VL Disease progression Death Adverse events		weeks. 10% lost-to-follow-up. Median 47.9 weeks.
	ID:498 Staszewski, 1999[126]	(Ongoing)	Asymptomatic or mildly symptomatic; CD4 > 50 VL >10,000	15% had previous ZDV	450 Mean CD4 = 345 Mean VL = 4.7	1.Ind (2400mg) + ZDV (600mg) + Lam (300mg) 2.Efa (600mg) + ZDV (600mg) + Lam (300mg) 3. Efa (600mg) + Ind (3000mg)	148 154 148	Plasma VL	NS	Intended 48 weeks.
CHEESE	ID:428 Cohen Stuart, 1999[52]	Main analysis	Age >18 HIV-1 RNA >10,000 or CD4 <500 or CDC B or C	4% had prior	70 (63/7) Mean age 38 Mean CD4 = 306 Median VL = 5.0, 4.98	1.Ind (2400mg) + ZDV (600mg) + Lam (300mg) 2. Saq-sgc (3600mg) + ZDV (600mg) + Lam (300mg)	35 35	CD4 count Plasma VL Dis prog Death Adverse events	NS	93% completed 24 weeks of study trt
EARTH-1	ID:501 Garcia, 1999[93]	Main analysis	Adults CD4 >500 VL ≥ 10,000	None	159 (115/44) Mean age 33 Mean CD4 = 632 Mean VL = 4.55	1.No treatment (after 10mths offered triple) 2.ZDV (500mg) + Zalc (2.25mg) 3.ZDV (500mg) + Did (3-400mg) 4.Stav (60-80mg) + Did (3-400mg) 5.Stav (60-80mg) + Lam (300mg) + Rit (1200mg)	32 29 32 33 33	CD4 count Plasma Viral load Disease progression Resistance CD4/CD8 ratio VL in CSF & tonsillar fluid	Change to another therapy if: severe intolerance/side effects; if VL has not decreased by >0.5log after 3 mths.	Intended 52 weeks. 5% lost to follow-up
PROAB 2002	ID:502 Haubrich, 1999[94]	Main analysis	Age ≥ 18 CD4 ≥ 150 and VL ≥10,000	28.6% had prior ZDV or Zalc.	84 (67/17) Median age 33-37.5 Median CD4 = 403 Median VL = 4.8 CDC A = 52% B = 39% C = 6%	1.ZDV(600mg) + Lam(300mg) + Amp (1800mg) 2. ZDV(600mg) + Lam(300mg) + Amp (2100mg) 3.ZDV(600mg) + Lam(300mg) + Amp (2400mg) 4.ZDV(600mg) + Lam(300mg)	21 22 21 20	Plasma VL CD4 count Adverse events	NS	12 weeks (followed by Amp addded to dual therapy)

Table 7d Study Characteristics: quadruple versus anything

Trial identifier	*Study*	*Type of report*	*Criteria*	*Prior antiretroviral treatment*	*Study population at baseline N (M/F)*	*Intervention (dose per day)*	*n*	*Outcomes*	*Stop criteria*	*Follow*
QUATTRO	ID:432 Anon, 1999[51]	Main analysis	Age ≥ 18 CD4 50-350	No	100 (92/8) Mean age 37 Median CD4 = 170 Mean VL = 4.9 Asymptomatic = 43% Symptomatic = 35% AIDS = 22%	1.ZDV (500mg)+Lam (300mg)+Lov (300mg) + Zalc (2.25mg) **T4** 2.Cyclical ZDV-Lam-Lov-Zalc; 8 wks each **C4** 3. ZDV (500mg) + Lam (300mg) **T2**	34 34 32	CD4 count Plasma VL Disease progression Death Adverse events Resistance Weight change	Patient or clinician wish	All comple 64 weel At 32 weeks, 76%, 9 still on allocate
Kirk	ID:454 Kirk, 1999[46]	Naïve stratum	Age >18 CD <200-300 or HIV RNA >100,000 or HIV-related symptoms	No	119 (103/16) Median age 39 Median CD4 = 110 Median VL = 5.3 AIDS = 24%	1.Ind (2400mg) + 2NAs 2.Saq (800mg) + Rit (1200mg) + 2NAs 3.Rit (1200mg) + 2NAs 2NAs = usually ZDV + Lam	38 42 39	CD4 count Plasma VL Adverse events Disease progression Death	NS	>90% followe for 24 v

Key to tables

NS = Not Stated
CD4 = CD4 count given in cells per µl
VL = plasma HIV viral load (log copies per ml)
QOL = Quality of Life

13.2 Search strategy to identify Randomised Controlled Trials (MEDLINE)

Source: Dickersin, Scherer and Lefebvre[40] and York CRD handbook[41]

#1 randomized controlled trial.pt.
#2 randomized controlled trials.sh
#3 random allocation.sh.
#4 double blind method.sh.
#5 single blind method.sh.
#6 1 or 2 or 3 or 4 or 5
#7 animal.sh.
#8 human.sh.
#9 7 not (7 and 8)
#10 6 not 9
#11 clinical trial.pt.
#12 exp clinical trials.sh.
#13 (clin$ adj3 trial$).ti,ab.
#14 ((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
#15 placebos.sh.
#16 placebo$.ti,ab.
#17 random.ti,ab.
#18 research design.sh.
#19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
#20 19 not 9
#21 20 not 10

13.3 Calculating standard deviations

From standard errors:	SD = $\sqrt{n}$ x SE
From 95% confidence intervals	SD = $\sqrt{n}$ x (upper limit – lower limit)/(2 x 1.96)
From interquartile ranges	SD = (UL-LL)/(2 x 0.67)
From t tests	Pooled SD = $\sqrt{(n_1 n_2/(n_1+n_2)}$ x diff in means/t
From exact p values	Convert p values to t values and repeat above step

13.4 Detailed rules of data extraction and manipulation

Naïve
Trials defined as naïve if one of the following:

- 70% of the patients had less than 6 months prior therapy
- When stratified, results of a naïve stratum given

Length of trial (timepoint)
For CD4 count and viral load, the timepoint taken was the longest time at which each arm had at least 50% of the starting population recorded.

N numbers
If numbers at outcome are not given, n at the start taken.

Medians given (CD4 count/viral load)
If mean change is not given, only median, then assume that median = mean.

Standard deviations
If standard deviation of the change is not given, use end mean with SD.

Graphical data
Data was taken from graphs if not given in the text or in tabular form. Data was measured to the nearest 0.5mm.

Dropouts
Defined as all those who started treatment but who discontinued the study for reasons other than reaching a trial endpoint or an adverse event. Given as % dropout over the total who started treatment.

13.5 Codes for meta-regression

Drug code

0 = placebo/no treatment
1 = ZDV
2 = Did
3 = Zalc
4 = Stav
5 = Saq
6 = Lam
7 = ZDV + Did
8 = ZDV + Zalc
9 = ZDV + Lam
10 = ZDV + Del
11 = Did + Del
12 = ZDV + Nev
13 = ZDV + Saq
14 = Stav + Lam
15 = Did + Lam
16 = Stav + Did
17 = Efa + Ind
18 = Stav + Lam + Rit
19 = ZDV + Lam + Amp
20 = Efa + ZDV + Lam
21 = Ind + ZDV + Lam or Ind + 2NAs
22 = ZDV + Lam + Lov
23
24 = Rit + 2NAs
25 = ZDV + Lam + Saq
26 = ZDV + Did + Nev
27 = ZDV + Did + Del
28 = Rit + Saq + 2NAs
29 = ZDV+Lam+Lov+Zalc
30 = other

Code for drug dose

0 = standard dose
1 = low dose
2 = high dose

Code for quality questions

(randomisation allocation/double blind)
0 = No
1 = Not clear
2 = Yes

Code for type of measure used

0 = mean change
1 = median change
2 = end mean
3 = end median

Code for double combinations comparisons

1 = Double vs ZDV
0 = other

13.6 STATA variable list

arm	Drug names (treatment arm)
drugdose	Dose of drug (treatment arm)
drugcode	Code for drug/combination (treatment arm)
basecd4	Baseline CD4 count (treatment arm)
ncd4	Number of patients with CD4 count (treatment arm)
cd4chang	Change in CD4 count (treatment arm)
cd4sduse	SD of CD4 change
tcd4	CD4 count timepoint
cd4type	Type of CD4 measure (mean/median etc)
basevl	Baseline viral load (treatment arm)
nvl	Number of patients with viral load data (treatment arm)
vlchange	Change in viral load (treatment arm)
vlsdused	SD of viral load change (treatment arm)
vlsens	Sensitivity of viral load assay
tvl	Viral load timepoint
vldropou	Viral load % dropout (treatment arm)
nprog	Number of patients showing disease progression/death (treatment arm)
nstart	Number of patients entered (treatment arm)
tprog	Duration of trial (treatment arm)
dropout	% dropout (treatment arm)
blind	Code for blinding
rand	Code for randomisation
conarm	Drug names (control arm)
condrugd	Dose of drug (control arm)
condrugc	Code for drug/combination (control arm)
conbasec	Baseline CD4 count (control arm)
conncd4	Number of patients with CD4 count (control arm)
concd4ch	Change in CD4 count (control arm)
concd4sd	SD of mean CD4 change (control arm)
conbasev	Baseline viral load (control arm)
connvl	Number of patients with viral load data (control arm)
convlcha	Change in viral load (control arm)
convlsdu	SD of change in viral load (control arm)
connprog	Number of patients showing disease progression/death (control arm)
connstar	Number of patients entered (control arm)
condropo	% dropout (control arm)
logordp	log odds ratio (disease prog)
selgordp	Standard error log odds ratio (disease prog)
sediff	Standard error of the mean difference
meandiff	Mean difference

13.7 STATA results: Meta-regression of disease progression/death (monotherapy versus placebo)

τ^2 (random effects meta-analysis) = 0.063

Baseline CD4 count (treatment arm) $\tau^2 = 0.000$

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
baseline CD4	.0003792	.0007185	0.528	0.598	-.001029	.0017874
_cons	-.6121952	.2856502	-2.143	0.032	-1.172059	-.0523312

Duration of trial (weeks) $\tau^2 = 0.000$

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
duration	.00614	.0015459	3.972	0.000	.00311	.0091699
_cons	-1.025919	.1854154	-5.533	0.000	-1.389326	-.6625112

Percentage dropout (Treatment arm) $\tau^2 = 0.0436$

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
dropout	-.0148538	.0138762	-1.070	0.284	-.0420506	.0123431
_cons	-.2899247	.2107522	-1.376	0.169	-.7029914	.1231421

Baseline CD4 count (Control arm) $\tau^2 = 0.000$

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Baseline CD4	.0003786	.0007225	0.524	0.600	-.0010374	.0017946
_cons	-.6111309	.2854921	-2.141	0.032	-1.170685	-.0515768

Percentage dropout (control arm) $\tau^2 = 0.0310$

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Dropout	-.0219103	.0132239	-1.657	0.098	-.0478286	.0040081
_cons	-.1706558	.2054122	-0.831	0.406	-.5732564	.2319447

Drug dose (treatment arm) $\tau^2 = 0.0664$

Idrugd_0-2 (naturally coded; Idrugd_0 omitted)

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]

```
---------+--------------------------------------------------------------------
Idrugd_2 |   .0686922   .3253766      0.211   0.833      -.5690341    .7064185
   _cons |  -.5608872   .2992051     -1.875   0.061      -1.147318     .025544
------------------------------------------------------------------------------
```

Blinding $\tau^2 = 0.0683$

```
i.blind       Iblind_0-2   (naturally coded; Iblind_0 omitted)

------------------------------------------------------------------------------
         |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
Iblind_2 |   .0338772   .7221814      0.047   0.963      -1.381572    1.449327
   _cons |  -.5366263   .7121426     -0.754   0.451        -1.9324    .8591475
------------------------------------------------------------------------------
```

Randomisation allocation $\tau^2 = 0.0732$

```
i.rand        Irand_1-2    (naturally coded; Irand_1 omitted)

------------------------------------------------------------------------------
         |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
---------+--------------------------------------------------------------------
 Irand_2 |  -.0860645     .24372     -0.353   0.724      -.5637469    .3916179
   _cons |  -.4697649   .1575459     -2.982   0.003      -.7785493   -.1609806
------------------------------------------------------------------------------
```

14 References

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