Articles

Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection

*Concorde Coordinating Committee**

Summary

Concorde is a double-blind randomised comparison of two policies of zidovudine treatment in symptom-free individuals infected with human immunodeficiency virus (HIV): (a) immediate zidovudine from the time of randomisation (Imm); and (b) deferred zidovudine (Def) until the onset of AIDS-related complex (ARC) or AIDS (CDC group IV disease) or the development of persistently low CD4 cell counts if the clinician judged that treatment was indicated.

Between October, 1988, and October, 1991, 1749 HIV-infected individuals from centres in the UK, Ireland, and France were randomly allocated to zidovudine 250 mg four times daily (877 Imm) or matching placebo (872 Def). Follow-up was to death or Dec 31, 1992 (total 5419 person-years; median 3·3 years) and only 7% of the 1749 had not had a full clinical assessment after July 1, 1992. Of those allocated to the Def group, 418 started zidovudine at some time during the trial, 174 (42%) of them at or after they were judged by the clinician to have developed ARC or AIDS (nearly all confirmed subsequently) and most of the remainder on the basis of low CD4 cell counts. Those in the Imm group spent 81% of the time before ARC or AIDS on zidovudine compared with only 16% for those in the Def group.

Despite the large difference in the amount of zidovudine between the two groups and the fact that the number of clinical endpoints (AIDS and death) in Concorde (347) outnumbers the total of those in all other published trials in symptom-free and early symptomatic infection, there was no statistically significant difference in clinical outcome between the two therapeutic policies. The 3-year estimated survival probabilities were 92% (95% CI 90–94%) in Imm and 94% (92–95%) in Def (log-rank p = 0·13), with no significant differences overall or in subgroup analyses by CD4 cell count at baseline. Similarly, there was no significant difference in progression of HIV disease: 3-year progression rates to AIDS or

death were 18% in both groups, and to ARC, AIDS, or death were 29% (Imm) and 32% (Def) (p = 0·18), although there was an indication of an early but transient clinical benefit in favour of Imm in progression to ARC, AIDS, or death. However, there was a clear difference in changes in CD4 cell count over time in the two groups. Median changes from baseline at 3 months were +20 cells/μL (Imm) and −9 cells/μL (Def), a difference of 29 cells/μL (95% CI 16–42; p < 0·0001) which persisted for up to 3 years. Thus such persistent differences in CD4 cell count do not necessarily imply long-term differences in clinical outcome.

6 participants had life-threatening adverse events that were judged to be possibly drug related: 4 occurred on trial capsules before unblinding (3 on zidovudine, 1 on placebo) and 2 occurred on open zidovudine. Despite a daily dose of 1 g of zidovudine, the frequency of severe haematological and other adverse events on trial therapy was low but significantly higher in the Imm group: 16 Imm and 2 Def participants stopped trial drug for haematological events and the estimated proportions with haemoglobin dropping below 10 g/dL were 5% and 1%, respectively, at 1 year and 8% and 2%, respectively, at 3 years. Another 83 (9%) Imm and 36 (4%) Def participants stopped for other adverse events, predominantly gastrointestinal or neurological symptoms (headaches) or malaise.

The results of Concorde do not encourage the early use of zidovudine in symptom-free HIV-infected adults. They also call into question the uncritical use of CD4 cell counts as a surrogate endpoint for assessment of benefit from long-term antiretroviral therapy.

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Introduction

Zidovudine inhibits the human immunodeficiency virus (HIV) reverse transcriptase enzyme and terminates proviral DNA chain synthesis in vitro. In the first placebo-controlled trial of this agent in individuals with advanced AIDS-related complex (ARC) or AIDS, there was a significant reduction in mortality and in the frequency of opportunistic infections over an average follow-up of 4 months.[1] The hope was that use of zidovudine earlier in infection might delay disease progression and therefore further improve survival. In Concorde, a randomised double-blind trial, two policies for use of zidovudine were compared in symptom-free individuals with HIV infection in terms of mortality, progression to ARC or AIDS, and safety and tolerability of the drug. In the immediate group (Imm), zidovudine was given immediately after randomisation; in the deferred group (Def), who received

placebo after randomisation, use of zidovudine was delayed. Zidovudine was to be started at the onset of either ARC or AIDS, because this was standard practice at the initiation of the trial. However, in October, 1989, after the results of two US trials,[2,3] clinicians were given the option of prescribing zidovudine on the basis of persistently low CD4 cell counts if they judged that treatment was indicated. Indications for starting zidovudine in the Def group were thereby made more flexible to maintain the clinical relevance of the trial. First results were reported in April, 1993.[4] This article describes the main clinical findings up to Dec 31, 1992; more detailed accounts of surrogate markers and adverse events are in preparation.

Participants and methods

Participants

Symptom-free HIV-antibody-positive individuals aged over 13 years were eligible with the following exclusions: (a) pregnant or breastfeeding; (b) use of immunomodulating or antiviral drugs (except acyclovir) within 3 months of trial entry; (c) weight less than 40 kg; (d) Karnofsky performance score less than 90; (e) plasma creatinine more than 150 μmol/L; (f) hepatic enzyme concentrations (aspartate or alanine aminotransferase) more than 5 times the upper limit of normal; (g) haemoglobin less than 12 g/dL (males) or less than 11 g/dL (females); (h) platelet count less than 100×10^9/L; (i) neutrophil count less than 1.5×10^9/L. Ethical committee approval was obtained for all participating clinical centres and all participants gave written informed consent.

Trial design and treatment

The original plan was to recruit 2000 individuals and follow them for 3 years. With this number and on the assumption of a 15% 3-year progression rate to ARC or AIDS, the trial would have a reasonable chance of detecting a one-third relative reduction in this rate of progression (80% power, 5% significance level, 2-tailed test),allowing for some non-compliance.

Randomisation by the national trials centres was by telephone for forty centres (UK and Ireland) and by Minitel for thirty-four centres (France). Randomisation was stratified by centre, and in the UK and Ireland balanced by minimisation[5] for CD4 count (> 400 or $\leqslant$ 400) and p24 antigen status (positive or negative) in the eighteen centres that recruited more than 12 participants.

Participants were randomly allocated either to zidovudine capsules (250 mg four times daily) (Imm group) or to placebo (Def group). Trial therapy could be modified for adverse events according to protocol guidelines. Participants were to start open zidovudine when they developed ARC or AIDS or, after a protocol amendment in October, 1989, on the basis of persistently low CD4 cell count (< 500/μL on two consecutive counts) if the clinician judged that treatment was indicated. Primary prophylaxis for *Pneumocystis carinii* pneumonia (PCP) was also allowed from October, 1989.

Participants and clinicians were blinded to the randomised treatment throughout all stages of the trial. Only well-matched batches of placebo and active drug were used. Each clinical centre instituted a procedure, regularly reviewed by members of the trials centres, to ensure that clinicians were blind to mean corpuscular volume (MCV). The randomisation code was broken only when essential for clinical management (in 4 participants for adverse events and in 28 to decide on alternative antiretroviral treatment after the results of a trial of didanosine in the USA (ACTG 116B/117),[6] but the trial physicians and principal investigators remained blind to the allocation.

Follow-up

Clinical assessment was carried out 4 weeks before and at randomisation, 4-weekly thereafter for the first year, and then every 12 weeks. All adverse events and medications were recorded. Case-report forms at each assessment were sent to the national trials centres and a sample was validated against participants' hospital notes. Some participants who had been lost to follow-up

were traced through the national AIDS registry (UK) and the death registries at town halls (France). Follow-up and assessment of all participants continues, irrespective of drug compliance or disease state, even though the blinded phase of the trial ended in March, 1993. Clinical information recorded at randomisation, adverse events, and protocol endpoints were reviewed by the trial physicians, who were blind to the randomisation.

Laboratory measurements

Full blood count, urea or creatinine, and liver enzyme concentrations were measured routinely at every clinical assessment, and serum was stored for p24 antigen and beta-2 microglobulin. (Full blood counts were also done at week 2, 6, and 10.) T-cell subsets were measured, largely by flow cytometry, 4 weeks before entry, at randomisation, and then every 12 weeks; all laboratories participated in national quality control schemes.[7] In 23 centres, cells and plasma were stored for further studies to include assessment of resistance. Serum p24 antigen was assayed in batches by use of a standard curve based on the HIV-1 p24 antigen quantification panel (Abbott Laboratories). Beta-2 microglobulin was assayed with a radioimmunoassay (Pharmacia). Concentrations of zidovudine and its glucuronide were measured in a cross-sectional sample of participants by high-performance liquid chromatography.[8,9]

Clinical endpoints

Primary endpoints were survival, serious adverse events, and progression to AIDS and to CDC group IV disease (ARC or AIDS). An independent group established criteria for the classification and timing of endpoints and, blinded, reviewed all deaths and those AIDS endpoints that did not fit these criteria. Deaths not classified as definitely HIV-related or drug-related were subsequently reviewed by the principal investigators, blinded, and classified as either possibly or unlikely to be HIV or drug related, although it was often difficult to be certain in the latter group. All ARC events were reviewed by the trial physicians and a sample of events by the principal investigators; all remained blind to individual allocations.

AIDS and ARC were defined as follows:

AIDS (based on the 1987 CDC classification[10])

i)	IVA1 (HIV wasting syndrome): unexplained weight loss (10% of body weight in < 6 months, 15% in < 9 months, or 20% in < 12 months) *and* either unexplained fever (persisting for more than 14 consecutive days or more than 15 days in a 30-day period) *or* unexplained diarrhoea (> 2 liquid stools per day for more than 30 days).
ii)	IVB1: encephalopathy (unexplained dementia)
iii)	IVC1[10]
iv)	IVD[10]
v)	IVE1: central nervous system disease of indeterminate aetiology

ARC

i)	IVA2: constitutional symptoms of both fever and diarrhoea as defined above
ii)	IVB2: myelopathy or peripheral neuropathy
iii)	IVC2: minor opportunistic infections defined as pulmonary or isolated cervical lymph node tuberculosis or severe and/or recurrent oral candidosis (reclassified to include only severe) or clinically definite, and persistent oral hairy leucoplakia (reclassified to include only moderate or severe). Severe oral candidosis was defined by a clinical description of severe, florid, marked, or plaques seen and/or extent as extensive or involving the palate and/or persisting despite treatment or relapsing after treatment. Oral hairy leucoplakia was defined as moderate if clinically definite and persisting for 2 or more consecutive visits or as severe if described as extensive, marked, or symptomatic, and/or bilateral, and/or requiring treatment with acyclovir. Reclassification was undertaken because of differences in interpretation between the clinical centres; all cases of oral candidosis and oral hairy leucoplakia were reviewed. Herpes zoster was not included because of the difficulty of distinguishing between single and multidermatomal disease.
iv)	IVE2: single constitutional symptoms of weight loss, fever, or diarrhoea as defined above or other disease possibly attributed to HIV including Hodgkin's lymphoma.

For comparison with ACTG 019,[2] advanced ARC was defined as two consecutive CD4 cell counts less than 200/μL and at least two signs or symptoms of ARC (IVA2 or IVC2, but including herpes zoster).

Statistical methods

Baseline values of laboratory tests were calculated as the mean of all pretreatment results taken no more than 3 months before randomisation. For the few participants with no results for one or

more tests within this period, the nearest pretreatment result to randomisation was used. Analyses at the specified post-randomisation assessment times were based on the mean of all values within a period of 6 weeks either side of the assessment date. For the MCV assessments, the within-person standard deviation was calculated by use of all baseline values for those participants (the majority) who had two or more results. For each subsequent assessment the change for each individual from his or her baseline value was related to its standard error (SE) calculated from the within-person standard deviation and the number of values at baseline and at that assessment.

Zidovudine exposure in each group was described in terms of (a) proportion of participants on zidovudine by follow-up time and (b) distribution of the time on zidovudine as a proportion of total follow-up time. Time on zidovudine before progression to ARC or AIDS (or to the last assessment date in those who did not progress) was analysed in the same way.

Comparisons of clinical endpoints and laboratory-determined adverse events involved time-to-event analyses by use of Kaplan-Meier plots and log-rank methods.[11,12] The frequency of other adverse events was compared by means of χ^2 test.

As secondary analyses, the possibility of time-dependent treatment effects, when indicated by the Kaplan-Meier plot, was explored by examining the separate contributions to the overall log-rank statistic from various periods of follow-up, as well as by formal modelling of the relative risk by use of proportional hazards regression models.[13]

Changes in CD4 counts were analysed by (a) comparing group medians at certain times; (b) constructing summary statistics with individual averages over follow-up (based on area under the CD4 curve) and individual slopes (based on both least squares and least absolute deviations methods); and (c) Kaplan-Meier and log-rank analyses of time to CD4-defined events.

Since the aim of the trial was to compare two treatment policies (Imm or Def), all analyses, except those of adverse events and compliance, were based on intention to treat. All p values reported are 2-tailed.

Trial management

The Data and Safty Monitoring Committee (DSMC) reviewed summary data on the primary endpoints every 4–6 months, mainly to assess toxicity, and reviewed two full interim analyses. The protocol specified that the DSMC should report to the chairmen of the Coordinating Committee if at any time or for any category of participants there was "clear evidence" of benefit (in terms of overall prognosis) or new information (eg, results obtained from other studies), that might significantly alter clinical practice. The statistical and biological criteria for "clear evidence" were not specified precisely and were left to the discretion of the DSMC.

In October, 1989, after the early termination of a trial in the USA (ACTG 019),[2] the Coordinating Committee and DSMC allowed an extension of the indications for the use of open zidovudine. Although the original policy to defer its use until ARC or AIDS was still encouraged, clinicians had the discretion to start open zidovudine (250 mg four times daily) in participants who had been enrolled in the study for more than 6 months and who had persistently low CD4 cell counts (at least two consecutive counts of less than 500 cells/µL at least 1 month apart), if they judged that such treatment was indicated clinically. Of the 1749 participants, 1138 (65%) were randomised before this amendment.

The Coordinating Committee also decided that primary prophylaxis for PCP should be allowed from October, 1989, to reflect current clinical practice.[14] No specific policy or regimen was recommended but clinical centres were asked to follow their standard approach for all patients.

Although the Coordinating Committee recognised that the changes meant that use of open zidovucine would need to be described in relation to CD4 cell counts as well as to the onset of symptomatic HIV disease, the protocol amendments were not thought to alter the aim of the trial or its ability to provide a valid comparison between the effects of the policies of immediate and deferred zidovudine treatment in patients taking the best available concomitant treatment.

	Imm (n = 877)	Def (n = 872)
Mean age in years (SD)	32 4 (9 2)	32 2 (8 3)
Percentage female	15%	16%
CD4 cell count per µL		
Total with results	865	861
≤200	5%	7%
201–	22%	24%
351–	31%	28%
>500	42%	41%
CD4 percentage		
Total with results	820	819
≤10	4%	5%
11–	31%	30%
21–	39%	38%
>30	26%	27%
p24 antigen positive (no tested)	14% (777)	14% (771)
β2 microglobulin > 2·4 µg/L (no tested)	58% (830)	59% (827)
Mean haemoglobin (g/dL) (SD)		
Male	14 8 (1 1)	14 7 (1 0)
Female	13 1 (1 1)	13 3 (1·2)

Table 1: **Baseline characteristics**

The Coordinating Committee decided to terminate the blinded phase of the trial when the median follow-up was over 3 years and the total follow-up time approached 6000 person-years. This decision was not based on a recommendation by the DSMC, but was taken because of considerable pressure from participants and physicians to be unblinded, especially among those who wished to consider alternative antiretroviral therapy.

Results

Between Oct 1, 1988, and Oct 31, 1991, 1761 individuals were randomised (892 in the UK and Ireland, 869 in France); 33 (45%) centres recruited more than 20 patients. Data up to Dec 31, 1992, are reported here. 12 of the 1761 were excluded: 5 were ineligible (HIV negative [1], symptomatic HIV disease [2], abnormal liver function tests [2]) and 7 were randomised in error before they had confirmed their consent. 1 participant was randomised twice and is included in his first randomisation group. The report is therefore based on 1749 individuals (877 Imm and 872 Def) of whom 6 (4 Imm, 2 Def) never started trial capsules. 95 participants (46 Imm, 49 Def) had minor violations of the eligibility criteria because of abnormal laboratory results and/or weight but were included in the analysis. Total study follow-up was 5419 person-years (2717 Imm, 2702 Def); median follow-up was 3·3 years in both groups. 127 participants (55 Imm, 72 Def) had no formal clinical assessment after July 1, 1992, although 50 of them (25 Imm, 25 Def) were known to be alive after this date. On average, the 127 lost to follow-up had higher CD4 cell counts (53% above 500/µL), were younger (mean age 28 years), and were less likely to be p24 antigen positive (10%) at trial entry compared with the whole population.

Baseline characteristics

Clinical and laboratory characteristics of the two groups were similar, including those not shown in table 1. 49% of participants were aged 25–34 years; 15% were women; 62% were homosexual/bisexual men, 13% reported intravenous drug use and 13% heterosexual contact, 7% had received contaminated blood products; and the remaining 5% had multiple or other risk factors.

Compliance with blinded trial medication

The MCVs of all participants were measured repeatedly while they were taking the trial capsules. Baseline mean MCV was 90 fL (within-person standard deviation 1·7) in both groups. By 12 weeks, 85% of 779 Imm and 0·9% of 775

	Imm (n = 877)	Def (n = 872)
Person-years follow-up	2717	2702
On trial capsules		
At last trial assessment	312	239
At default	14	20
At death	7	3
Reasons for stopping trial capsules		
Progression to ARC or AIDS	91 (80)	114 (109)
Clinical evidence of progression, not confirmed*	8 (7)	19 (15)
Low CD4 count	137 (135)	204 (204)
Adverse events	99 (40)	38 (14)
Personal reasons	203 (62)	231 (74)
Other reasons	2 (0)	2 (1)
Never started trial capsules	4 (3)	2 (1)

*These participants were judged by their clinician to have developed ARC or AIDS but the diagnosis was not confirmed at independent review.
Figures in parentheses are numbers of patients who started open zidovudine (or didanosine) immediately or subsequently.

Table 2: **Status of trial and reasons for stopping trial capsules**

Def had an MCV more than 3 SE above baseline. The proportion remained between 87% and 92% for the Imm group (based on 308 at 132 weeks and 691 at 24 weeks) and between 1·4% and 3·5% for the Def group (based on 276 at 120 weeks and 227 at 132 weeks).

Serum concentrations of zidovudine and its glucuronide (GZDV) were measured in a cross-sectional sample of 414 (239 Imm, 175 Def) participants while they were taking the trial capsules. Detectable concentrations of GZDV (> 0·1 µmol/L) were found in 193 (81%) Imm participants, although in 2 this result was judged to be of doubtful significance (in 1 because the concentration of zidovudine was much higher than that of GZDV, and in the second the value of 28 µmol/L was thought to be due to assay interference). In the 46 (19%) Imm participants with no detectable GZDV (≤0·1 µmol/L), only 14 samples were collected within 6 hours of ingestion of trial capsules; this observation suggests non-compliance, although 4 of the 12 who had MCV results at the time of sampling had raised values. The timing of the samples in the remaining 32 (either not available [16] or more than 9 hours [16] precluded a definitive statement about compliance although the MCV was raised in 22 out of the 27 who had results. 6 (3%) Def participants had detectable concentrations of GZDV but 3 were thought to be of doubtful significance (2 had GZDV concentrations of 0·6 µmol/L but undetectable zidovudine about 1 hour after taking capsules, and 1 had zidovudine concentration that exceeded that of GZDV). None of the 6 had raised MCV values at the time.

	Imm	Def
	No (%)	No (%)
Never started	550 (63)	454 (52)
Started at or after confirmed ARC or AIDS	94 (11)	134 (15)
Started before confirmed ARC or AIDS, reason*		
Protocol progression before confirmed date†	21 (2)	16 (2)
Non-confirmed progression†	22 (3)	24 (3)
Low CD4 cell count‡		
≤200/µL	93 (11)	113 (13)
201–300/µL	49 (6)	83 (9)
>300/µL	46 (5)	43 (5)
Other reasons	2 (<1)	5 (<1)
Total	877 (100)	872 (100)

*Includes 4 participants (2 Imm, 2 Def) reported to have started at their last assessment. In some participants the reason for starting open zidovudine differed from the reason for stopping trial capsules (given in table 2)—eg, participants who stopped for adverse events or personal reasons may have subsequently progressed or started because of low CD4 cell counts.
†Participants were judged by their clinician to have ARC or AIDS which was only confirmed as a protocol defined endpoint at a later date or was not confirmed.
‡With or without HIV-related symptoms not fulfilling a protocol definition of ARC or AIDS; most recent CD4 count before starting open zidovudine.

Table 3: **Open zidovudine use**
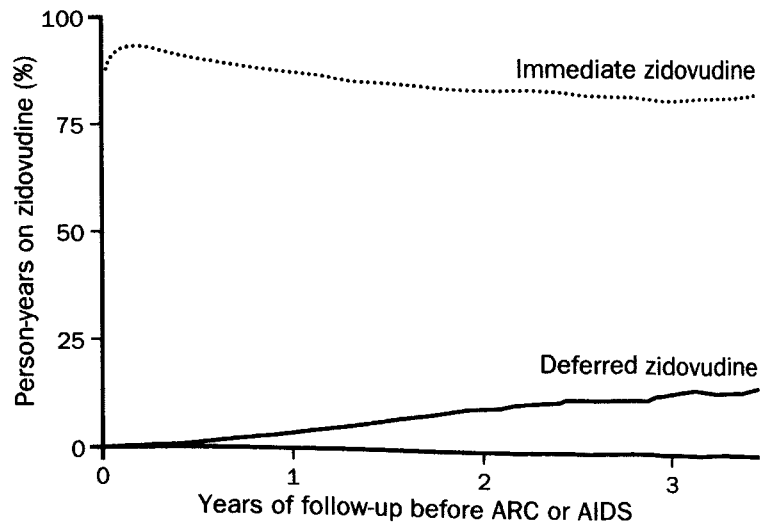
Total trial time (person-years)

Immediate	797	1284	1257
Deferred	752	1228	1155

Figure 1: **Percentage of person-years on zidovudine before ARC or AIDS by treatment group**
Not all participants started trial drug on the day of randomisation.

Zidovudine exposure

Table 2 summarises the status of the trial and gives details of participants who stopped trial capsules. In table 3 the reasons for starting open zidovudine are shown for both groups. For the Imm group this was a switch from zidovudine trials capsules to open-label drug and for the Def group this was the first time zidovudine was prescribed (before or after protocol-defined progression); neither group was to be unblinded to their original allocation. In some participants in both groups open zidovudine was started some time after they had stopped trial capsules for other reasons.

There was a substantial difference in the proportion of total trial time spent on zidovudine in the two groups (Imm 80%, Def 23%); the difference was even greater for the time before progression to ARC or AIDS, which was 81% and 16%, respectively. Figure 1 gives the proportion of time before ARC or AIDS spent on zidovudine over time; at 1 year the value is 87% for Imm and 3% for Def and at 3 years 83% and 14%, respectively.

Figure 2 shows, at each time point, the proportion of Def participants who were taking zidovudine and, for comparison, the proportion, who had progressed to ARC or
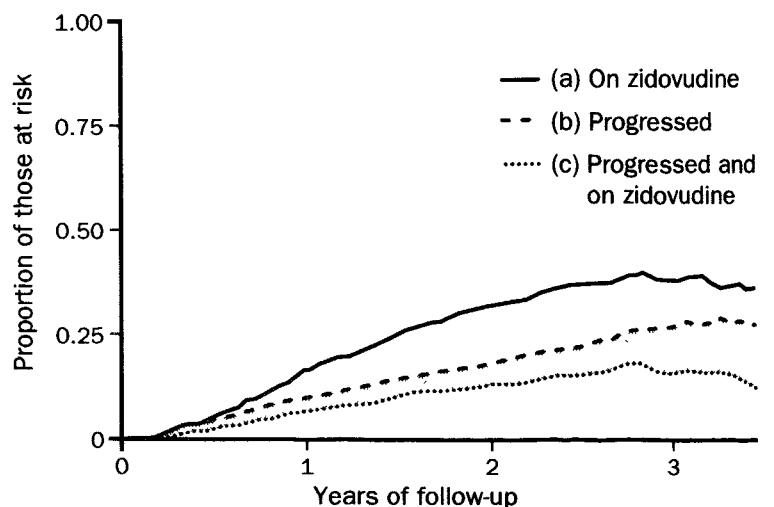

Figure 2: **Proportions of participants in deferred group on zidovudine (a), who had progressed to ARC or AIDS (b), and who had both progressed and were on zidovudine (c)**
At each point in time, the difference between (b) and (c) (shaded) represents the proportion who had progressed to ARC or AIDS but were not on zidovudine.
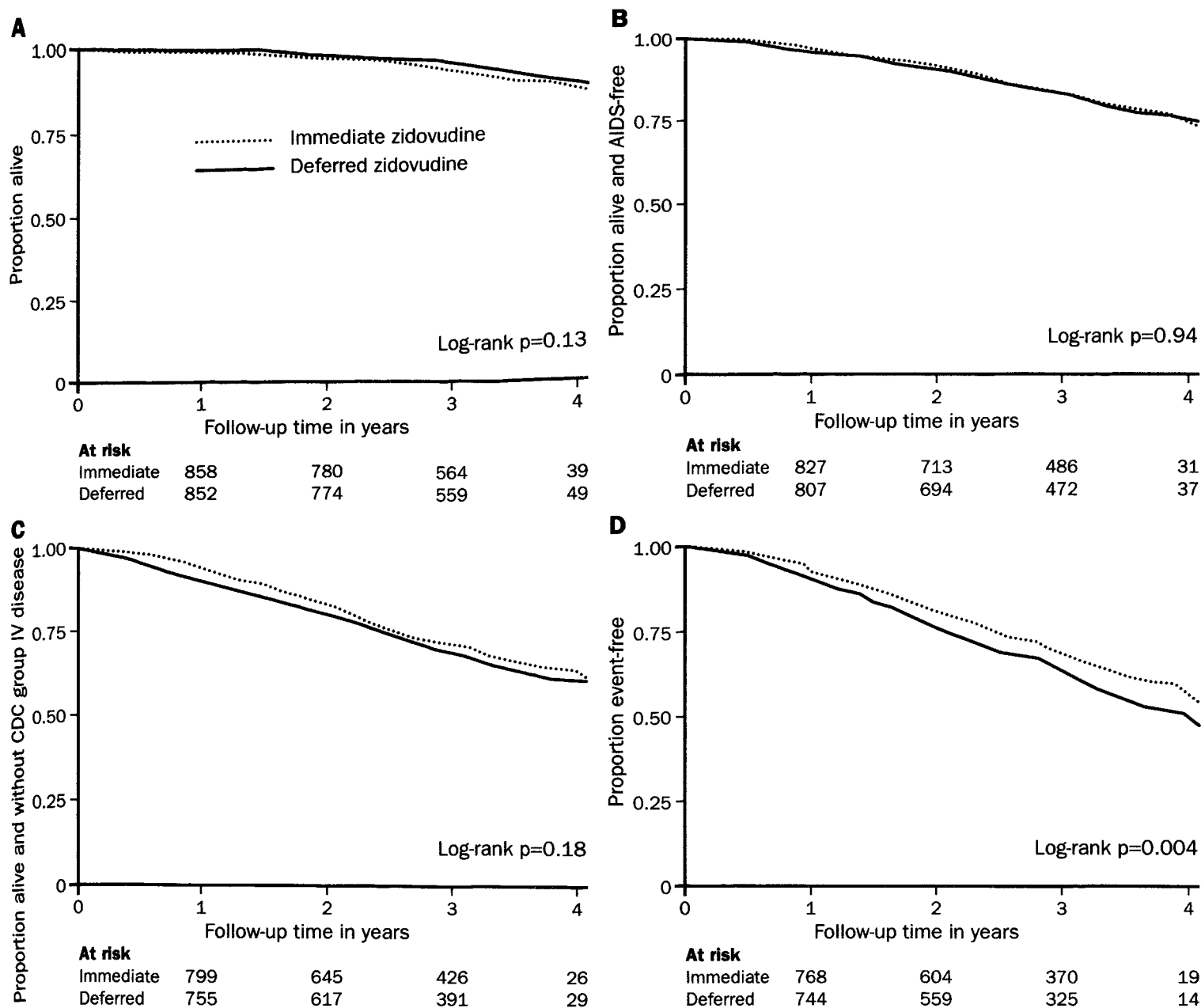
Figure 3: **Kaplan-Meier plots for all cause mortality (A), time to AIDS or death (B), time to ARC, AIDS or death (C), and time to a reduction in CD4 count to less than half of the baseline value or AIDS or death (3b plus the CD4 endpoint) (D)**

AIDS and the proportion who had both progressed and were on zidovudine. Of the 418 Def participants who started zidovudine at some time during the trial, 69% either started at or after progression to ARC or AIDS (as defined by the protocol) or the development of symptomatic disease judged by the clinician to be ARC or AIDS (but not all confirmed), or had CD4 counts of 200/μL or less (250/μL or less in 80% and 300/μL or less in 89%).

Time from randomisation to open zidovudine was significantly shorter in the Def group. The unadjusted relative rate of starting open zidovudine before ARC or AIDS (Imm/Def) was 0·71 (95% CI 0·60–0·84; p = 0·0001). After adjustment for current and baseline CD4 count in a Cox proportional hazards model, the relative rate was 0·82 (95% CI 0·69–0·98; p = 0·03). The distribution of the CD4 count at the time of starting in those who started open zidovudine before ARC or AIDS on the basis of CD4 count was similar in the two groups: 49% of 188 Imm and 47% of 239 Def had a CD4 count of 200/μL or less (table 3). In those who never started, the last CD4 count was less than 200/μL in 8% of both groups.

Survival and disease progression

A total of 172 (96 Imm, 76 Def) participants died; 22 (15 Imm, 7 Def) of the deaths were judged unlikely to be HIV-related or drug-related. For the 15 Imm participants the immediate cause was reported to be: 6 intravenous drug users died of overdoses (3) or from complications (1 renal failure secondary to an intra-arterial injection, 1 from inhalation of vomit, and 1 from a head injury related to an overdose); 4 died from malignant tumours (2 carcinoma bronchus and 1 rectum; 1 cerebral sarcoma); 3 further deaths were reported as being due to suicide (1), a road traffic accident (1), and drowning (1) and the remaining 2 were due to cardiovascular disease (1) and bleeding oesophageal varices (1). For the 7 Def participants; 1 intravenous drug user died from an overdose, 3 died from malignant tumours (2 carcinoma lung, 1 prostate); 2 further deaths were reported to be due to suicide (1) and a road traffic accident (1), and the remaining death was from cardiovascular disease. All deaths except 2 Imm (1 overdose, 1 varices) and 4 Def (3 malignant disease and 1 cardiovascular) occurred without a prior ARC or AIDS diagnosis.

Survival was not significantly different between the two groups (log-rank p = 0·13) (figure 3a). The crude death rates (per 100 person-years) were 3·5 Imm and 2·8 Def (table 4); the summary risk ratio (Imm/Def) was 1·26 (95% CI 0·93–1·70). The estimated 3-year probabilities of death were 8% Imm and 6% Def, an observed relative increase (Imm to Def) of 29% (95% CI −9% to +90%).

Clinical progression to	CD4 ≤200/µL				CD4 201–500/µL				CD4 >500/µL				No result		Total				Log rank p
	Imm (n=45)		Def (n=60)		Imm (n=460)		Def (n=449)		Imm (n=360)		Def (n=352)		Imm (n=12)	Def (n=11)	Imm (n=877)		Def (n=872)		
	No	Rate*	No	Rate*	No	Rate*	No	Rate*	No	Rate*	No	Rate*			No	Rate*	No	Rate*	
Death																			
Total	17	12 8	16	8 7	58	4 1	47	3 4	20	1 8	12	1 1	1	1	96	3 5	76	2 8	0 13
HIV related†	17	12 8	15	8 1	50	3·5	42	3 1	13	1 2	11	1 0	1	1	81	3 0	69	2 6	0 34
AIDS or death‡	31	29 8	32	22 9	111	8·5	103	8·2	33	3 1	33	3 2	1	3	176	7 0	171	6 9	0 94
ARC, AIDS, or death‡	38	44 6	39	33 9	170	14 1	176	15·9	56	5 5	63	6 4	3	6	267	11 3	284	12 7	0 18
Advanced ARC,AIDS or death‡	33	33 1	33	24 4	122	9 4	115	9 3	35	3 3	35	3 4	1	3	191	7 6	186	7 6	0 91

*per 100 person-years.

†Includes 6 deaths (4 Imm, 2 Def) possibly HIV-related or drug related and excludes 22 (15 Imm, 7 Def) unlikely to be HIV-related or drug related.

‡As first event.

Table 4: **Clinical endpoints: number and rate per 100 person-years by baseline CD4 count**

Progression to AIDS or death (figure 3b) was similar in the two groups: 176 Imm and 171 Def developed AIDS or died (p = 0·94). The summary risk ratio (Imm/Def) was 1·01 (95% CI 0·82–1·24) and the estimated 3-year probability of AIDS or death was 18% in both groups (95% CI for a relative increase Imm/Def − 20% to + 22%).

Progression to ARC, AIDS or death (267 Imm, 284 Def) was not significantly different between the two groups (figure 3c; p = 0·18). The estimated 3-year probabilities of progression to ARC, AIDS, or death were 29% Imm and 32% Def, a relative reduction of 9% (95% CI − 6% to + 22%) in favour of Imm. However, an analysis of data up to 1 year, undertaken on the basis of the Kaplan-Meier plot, indicated an early transient delay in favour of Imm (log-rank p for the first year 0·003), but this was not maintained (p > 0·75 for subsequent years) and was largely accounted for by a delay in progression to ARC. Fitting the relative risk of progression to ARC, AIDS, or death as a log linear function of follow-up time in a Cox proportional hazards regression model gave an estimated relative risk (Imm/Def) of 0·77 (95% CI 0·62–0·96) at 1 year and 0·85 (95% CI 0·71–1·01) at 18 months.

The findings were broadly similar when the analyses were stratified by baseline CD4 count (table 4) or by clinical centre, and when deaths judged unlikely to be related to HIV or its treatment were ignored. In the latter case, the log-rank p values were 0·34 for time to death, 0·68 to AIDS or death, and 0·07 to ARC, AIDS, or death. Significantly more participants died without developing ARC or AIDS from causes thought unlikely to be HIV-related or treatment related in the Imm group (13) than in the Def group (3) (p = 0·02). Another 9 (6 Imm, 3 Def) died before developing ARC or AIDS from causes thought to be (definitely or possibly) HIV-related.
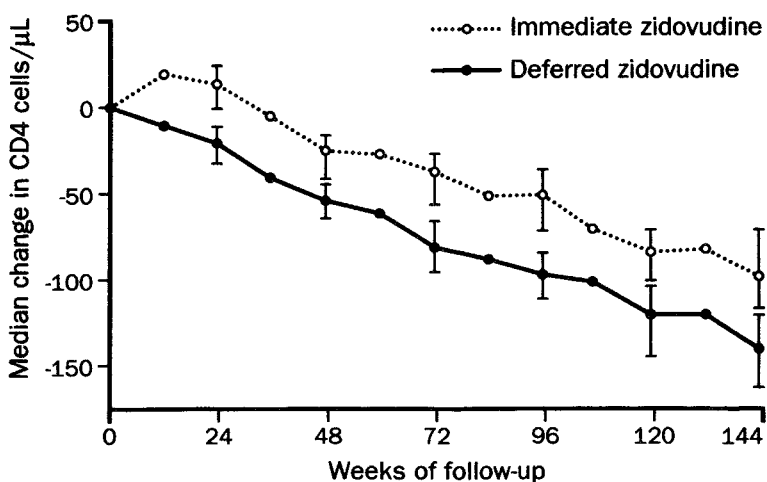
A further analysis restricted to participants fulfilling the eligibility criteria for the ACTC 019 study[2] and with similar endpoints (advanced ARC, AIDS, or death) was undertaken and overall there was no significant difference between the groups: summary risk ratio (Imm/Def) 1·04 (95% CI 0·83–1·31). In an analysis of events within 55 weeks of randomisation in this subgroup of participants, 24 of 505 Imm developed advanced ARC or AIDS or died vs 37 of 509 Def (p = 0·09). Additional exploratory analyses did not affect the main conclusion. For example, stratification by calendar time (before or after October, 1989) produced almost identical results. Details of the first ARC and first AIDS events are given in table 5 and were broadly similar in the two groups.

Changes in CD4 lymphocyte counts and percentages

There was a clear difference in the changes in CD4 count over time in the two groups (figure 4) with an initial median increase in CD4 count at 3 months in the Imm group (median 20 cells/µL) but a decline in the Def group (9 cells/µL) (95% CI for the difference 16–42; p < 0·0001). There was an overall shift of about 30 cells in the CD4 cell count distribution at 6 months in Imm compared with Def. Average rate of change in CD4 count, as cells per year, was measured by the mean of individual slopes for each group. Over the first 6 months, there was an increase of about 50 cells per year (+ 47, 95% CI 12–82) in the Imm group but a decrease of the same order (− 49, 95% CI − 79 to − 19) in the Def group. In the second 6 months there was a decrease in both groups which was greater in Imm (− 100, 95% CI − 158 to − 45) than in Def (− 64, 95% CI − 120 to − 8). In the second and third years there was a continuing decline which was similar in the two groups (− 59, 95% CI − 78 to − 39 for Imm and − 50, 95% CI − 78 to − 22 for Def in the second year). However, the difference in median change from baseline between the two groups of about 30 cells (34 at 24 weeks and 29 at 48 weeks) persisted for at least 3 years. Because of the persistent difference between the groups in CD4 count, analyses of time to CD4-defined endpoints such as a 50% drop from baseline (figure 3d) or time to a fixed value (eg, 350 or 200/µL) show a significant delay in the Imm group compared to the Def group.

Median changes in CD4 percentages from baseline values were small but were significantly different between the two groups. Based on numbers similar to those given in figure 4, the difference in median changes from baseline (Imm-Def) was 1% at weeks 12, 48, and 60, 2% at weeks 24 and 84, 3% at week 36, and 0% at week 132.

Further details of changes in surrogate markers including T cell subsets, p24 antigen, and β2 microglobulin will be reported separately.

Prophylaxis against PCP

613 participants (278 Imm, 335 Def) started PCP prophylaxis during the trial, 416 (195 Imm, 221 Def) before

Figure 4: **Median change from baseline in CD4 cell counts and pointwise 95% CI at 24-weekly intervals**

Number with results						
Immediate	721	695	643	592	557	482
Deferred	730	703	636	594	560	468

CDC group: AIDS	Imm	Def	Total
IVA1 (HIV wasting)	9	7	16
IVB1 (HIV encephalopathy)	6	7	13
IVC1			
Pneumocystis carinii pneumonia	42	39	81
Oesophageal candidosis	28	32	60
Cytomegalovirus disease	3	4	7
Cerebral toxoplasmosis	9	12	21
Cryptosporidial diarrhoea	6	5	11
Disseminated Mycobacterium avium intracellulare	3	3	6
Herpes simplex virus disease	4	0	4
Cryptococcal meningitis	2	1	3
Salmonella septicaemia	2	1	3
Isosporiasis	0	2	2
Extrapulmonary tuberculosis	2	2	4
Progressive multifocal leucoencephalopathy	1	2	3
Systemic candidosis	1	0	1
IVD			
Kaposi's sarcoma	27	41	68
Non-Hodgkins lymphoma	9	6	15
IVE1*	1	0	1
Total†			
Events	155	164	319
Patients	149	161	310

CDC group: ARC	Imm	Def	Total
IVA2			
Fever and diarrhoea	3	0	3
IVB2			
Neuropathy or myelopathy	5	3	8
IVC2			
Severe oral candidosis	68	74	142
Moderate or severe oral hairy leucoplakia	38	57	95
Pulmonary or cervical node tuberculosis	2	4	6
IVE2			
Weight loss	35	35	70
Diarrhoea	1	0	1
Other	10	11	21
Total‡			
Events	162	184	346
Patients	151	173	324

*AIDS-related central nervous system lesion (differential diagnosis: lymphoma or cerebral toxoplasmosis).
†319 events in 310 patients, 9 patients had two AIDS-defining conditions diagnosed on the same day.
‡346 events in 324 patients, 22 patients had 2 ARC events on the same day, 3 (2 Imm, 1 Def) had AIDS and ARC at the same time, and 105 (50 Imm, 55 Def) subsequently developed AIDS.

Table 5: **First AIDS and ARC events**

they developed ARC or AIDS. The most important determinant of when PCP prophylaxis should be started was a low CD4 count. Zidovudine, on average, slightly increased the CD4 count initially. In terms of time since randomisation, PCP prophylaxis was therefore started later in the Imm group. The unadjusted relative rate (Imm/Def) for starting PCP prophylaxis before ARC or AIDS was 0·78 (95% CI 0·64–0·95; p=0·01), but, as might be expected, there was no significant difference between Imm and Def when adjustment was made for CD4; the relative rate adjusted for baseline and current CD4 count was 0·93 (95% CI 0·76–1·13; p=0·4). In those who started PCP prophylaxis, the distribution of the nearest CD4 count before the start was similar in the two groups (200/μL or less in 62% of 278 Imm and 61% of 335 Def, and less than 300/μL in 88% and 89%, respectively).

Adverse events

6 participants had life threatening adverse events, 4 (3 Imm, 1Def) while taking trial capsules. The 3 Imm events were atypical erythroid (pro-erythroblastic) leukaemia (1); liver failure in a hepatitis C infected haemophiliac (1); pancytopenia and a subdural haematoma which resolved, in a haemophiliac (1). The 1 Def event was fatal hepatic failure while taking tricyclic antidepressants and placebo capsules. The other 2 participants were taking open zidovudine (1 Imm [fatal acute septicaemia in a haemophiliac who had undergone a splenectomy and who

Type of event	Action taken			
	Trial capsules stopped		Permanently reduced dose	
	Imm	Def	Imm	Def
Haematological	17	2	62	15
Gastrointestinal	52	20	53	13
Musculoskeletal	10	6	20	6
Neurological	27	15	24	6
Malaise	28	4	24	4
Hepatic	9	4	4	1
Other	8	10	13	3
Total events	151	61	200	48
Total patients*	99	38	148	37

*In 16 Imm and 2 Def patients the main reason for stopping trial capsules was haematological

Table 6: **Adverse events**

was taking penicillin prophylaxis] and 1 Def [fatal cerebral haemorrhage]).

In all, 99 Imm and 38 Def participants stopped trial capsules because of adverse events. In only 16 Imm and 2 Def was haematological toxicity the main reason; in the rest it was predominantly gastrointestinal or neurological symptoms (headache) or malaise (table 6). One or more blood transfusions were received by 18 Imm and 11 Def while they were taking trial capsules. Permanent dose reductions also occurred more often in the Imm group. Analyses of laboratory data showed significant differences in the time to development of anaemia and neutropenia between the groups; the estimated proportions with a haemoglobin of 10 g/dL or less were 5·3% Imm and 0·9% Def, respectively, at 1 year and 8·5% and 2·1% at 3 years. The corresponding figures with a neutrophil count less than $0·8 \times 10^9/L$ were 4·3% and 1·3% at 1 year and 8·7% and 2·6% at 3 years. 16 participants (10 Imm, 6 Def) stopped trial capsules because of muscle pain or weakness, 4 and 2, respectively, had raised serum creatine kinase concentrations. A detailed report of adverse events is under preparation.

Discussion

Concorde was originally designed to see whether zidovudine delayed the onset of symptomatic disease in symptom-free HIV-infected individuals and to compare two policies of therapy in terms of the effect on survival and disease progression. The policies were either immediate treatment (at the time of randomisation) or its deferral until the onset of ARC or AIDS or, after a protocol amendment, persistently low CD4 cell counts if the clinician judged treatment to be indicated. The protocol amendment inevitably shifted the emphasis to the policy comparison, but like the amendment allowing PCP prophylaxis, was pragmatic and flexible and ensured that the results of the trial would be relevant to current clinical practice. Consequently zidovudine exposure of the two groups had to be described carefully in relation to both clinical progression and CD4 cell count. Despite a large difference in the amount of zidovudine taken by the two groups, there was no statistically significant or clinically important benefit in terms of survival or disease progression from the immediate use of zidovudine compared with its deferred use over an average follow-up of 3 years. However, there was an indication of a transient delay in progression to ARC, AIDS, or death which was largely accounted for by a delay in progression to ARC.

There were no substantial biases in Concorde that could have concealed an important clinical effect. The two groups were well-balanced according to prognostic factors, the number of participants lost to follow-up for more than 6

months was small, placebo and zidovudine capsules were well matched, and the MCV results were blinded. Decisions about PCP prophylaxis largely follow guidelines that recommend starting therapy at about 200 CD4 cells/μL.[14] Thus in routine practice, because of the effect of zidovudine on the CD4 cell count, one result of its early use will be to delay slightly the start of PCP prophylaxis. Concorde, as is appropriate, reflects this delay. The decision to start PCP prophylaxis was made at a very similar CD4 cell count in both groups but the time from randomisation to starting was shorter in the Def group. This difference was explained by the sustained difference in CD4 cell count between the groups. The time to starting open zidovudine was also shorter in the Def group but most of the difference was again explained by the effect of zidovudine on the CD4 counts. Any residual differences could be due to the effect of adverse events while on trial capsules on the timing of starting open zidovudine, to the occurrence of early clinical symptoms or signs, or possibly to some unblinding or simply to chance alone. The main analysis was based on "intention to treat" rather than "on treatment" because the latter is subject to major biases and therefore loses the advantages of randomisation.[12] In particular, an "on treatment analysis" might have excluded a disproportionate number of progressors randomised to zidovudine, because both zidovudine toxicity and therefore treatment discontinuation increases with disease progression.

It is difficult to give one simple description of the criteria for zidovudine use in the patients randomised to deferred treatment because individual clinicians were left to use their own judgment, in the light of guidance given by the Coordinating Committee, to determine when to start. Some clinicians were influenced mainly by symptoms, some by low CD4 counts, and others by a combination of the two. Because of these differences, the timing of starting zidovudine was analysed in detail. It is clear that there was a substantial difference between the two groups in the amount of zidovudine received, especially before progression. It is questionable whether the limited exposure to zidovudine before ARC or AIDS in the Def group could have masked a sustained difference between immediate treatment and the original policy of deferred treatment until the onset of ARC or AIDS. If the efficacy of zidovudine in delaying the onset of symptomatic disease depends simply on its duration, irrespective of disease stage, the observed zidovudine exposure before ARC or AIDS in the Def group would have had a negligible effect. Alternatively, if the effect of zidovudine depends only on its being given before a threshold stage in disease progression (eg, a critical CD4 count), a sustained difference in efficacy between the two groups might have been missed. Of those in the deferred group who started open zidovudine before ARC or AIDS (confirmed or not), 82% did so at CD4 count of 300/μL or less, which indicates that such a threshold for intervention, if it exists, would probably occur below this concentration.

Although Concorde is the largest trial in symptom-free HIV infection in terms of the number of clinical events and length of follow-up, it is important to consider whether it could have missed any clinically important advantage or disadvantage to the Imm group. The 95% CIs around the estimated relative differences in event rates at 3 years indicate that Concorde is unlikely to have missed a relative reduction in progression to AIDS or death, or to ARC, AIDS or death of as much as 22% in the Imm group

compared with the Def group (eg, resulting in an absolute reduction from 32% to 25% for ARC, AIDS, or death). However, the observed relative increase in mortality in the Imm group (29%; an absolute increase from 6% to 8%) could have been much greater and a relative reduction of more than 9% is unlikely.

There was some evidence of a transient delay in progression to ARC, AIDS, or death although this was not significant over the full follow-up even when deaths not attributable to HIV or its treatment were ignored. Many of the relatively mild ARC endpoints, in particular oral hairy leucoplakia and oral candidosis, were difficult to assess and classify. There remains a suspicion that clinicians were more likely to diagnose ARC when CD4 counts were low, even though the change in protocol had the effect of unlinking the timing of the diagnosis of ARC from the timing of the clinician's decision to start open zidovudine. Since participants randomised to zidovudine maintained higher CD4 counts, it may be unwise to place too much emphasis on any apparent delay in progression to ARC.

The absolute frequency of adverse events was low despite the daily dose of 1g zidovudine but it was significantly higher in the Imm group. Most of the adverse events leading to discontinuation of trial capsules or permanent dose reduction were not haematological; nausea, vomiting, malaise, and headaches occurred most frequently. The estimated proportion of participants with severe anaemia (haemoglobin < 8g/dL) in the Imm group was 1·7% at 1 year, similar to the group receiving 500 mg a day in the ACTG 019 study (1·1%).[2] There was a low frequency of muscle pain and weakness. Although Concorde did not specifically address issues of the cost-effectiveness of the different policies or include measures of quality of life, more detailed information on the impact of adverse events will be the subject of a subsequent report.

The small but highly significant and persistent difference in CD4 count between the groups was not translated into a significant clinical benefit. Thus, analyses of the time until certain concentrations of CD4 were reached (eg, 200/μL, 350/μL, or 50% of baseline) revealed significantly shorter times in the Def group. Had such analyses been regarded as fundamental, the trial might have been stopped early with a false-positive result. This discrepancy in the differences between Imm and Def groups in terms of changes in CD4 count and of long-term clinical response casts doubt on the uncritical use of CD4 counts as "surrogate endpoints" in trials, although their value as a prognostic marker for disease progression in cohorts and trials is beyond dispute.[15-18] The reason for this discrepancy is unclear. Perhaps zidovudine shifts a proportion of poorly functioning CD4 cells into the circulating blood pool. Alternatively, the increase in CD4 cell count may be too small and transient to translate into a clinical benefit over 3 years. If other antiretroviral therapies were to induce a greater or more prolonged increase in CD4 count than that observed in Concorde they might have a greater clinical effect.

In one trial in the USA (VA 298: table 7), immediate and deferred zidovudine treatments were compared in individuals with early symptomatic disease and CD4 counts between 200 and 500/μL.[19] Treatment, in the deferred arm, was to be started at the onset of AIDS or at a CD4 count below 200 cells /μL. There was no significant difference between the two groups in survival or progression to AIDS or death after a mean follow-up of more than 2 years, although progression to AIDS was reported to have been delayed in the immediate treatment group when all deaths

Trial	Daily dose of zidovudine (mg)	CD4 count at entry (per µL)	Number in analysis		Average follow-up (months)	Number of events*			
						Death		AIDS or death	
			Z/Imm	P/Def		Z/Imm	P/Def	Z/Imm	P/Def
Early symptomatic infection									
ACTG 016[3]	1200	200–800	360	351	11	2	0	7	21
VA 298[19]	1500	200–500	170	168	28	23	20	38	48
Symptom-free infection									
ACTG 019[2]†	1500	<500	457	428	13	3	4	14	33
	500		453			1		11	
EACG 020[21]	1000	>400	495	489	21			6	9
ACTG 036[22]	1500	≤500	92	101	10	1	3	3	6
EA haemophilia[24]	1000	100–400‡	69	71	21§	0	0	5	4
EACG 017[23]	1000	200–400‡	167	162	22¶	6	7	11	12
Concorde	1000	Any	877	872	36	96	76	176	171

*The VA and Concorde trials compared immediate (Imm) and deferred (Def) use of zidovudine; the other trials compared zidovudine (Z) and placebo (P). †Two dose levels of zidovudine were included. ‡or p24 antigenaemia. §99 weeks Z, 80 weeks P. ¶60 weeks Z, 57 weeks P for AIDS or death.

Table 7: **Published placebo-controlled trials of zidovudine in symptom-free and early symptomatic infection**

before AIDS were censored. The efficacy of zidovudine compared with no treatment in early disease or symptom-free infection has been studied in six other placebo-controlled trials, summarised in table 7. Both ACTG 016[3] and ACTG 019[2] showed that, over an average follow-up of about 1 year zidovudine delayed progression to advanced ARC and AIDS. The results of Concorde, reanalysed with equivalent entry criteria, endpoints, and follow-up as for ACTG 019 are not inconsistent with these results. When the US study was terminated, zidovudine was offered to all placebo participants. For those participants who were followed up for a longer time it was reported that there was sustained benefit in the subgroup with CD4 cells above 300/µL but not in the remainder although there was no difference in survival in either group.[20] In the European/Australian study (020),[21] only 16 of 984 participants progressed to severe ARC or AIDS, partly because the study was not analysed on an intention to treat basis: data were censored 3 months after the termination of blinded study treatment. Other endpoints, therefore, were used to assess efficacy. Zidovudine was reported to slow the rate of development of CDC group IV disease, and clinical HIV disease (including oral candidosis, oral hairy leucoplakia, and herpes zoster not achieving the study definition of ARC, as well as ARC and AIDS) and to prolong the time to a CD4 count of less than 350/µL. If Concorde is reanalysed (on an intention to treat basis) according to equivalent entry criteria and a CD4 endpoint of less than 350/µL in addition to the Concorde defined endpoints of ARC, AIDS, or death, a highly significant difference is seen between the two groups in favour of immediate therapy, largely because of the effect of zidovudine on CD4 counts. The other three trials were smaller and were stopped early with inconclusive results.[22-24] The number of major clinical endpoints of AIDS and death in Concorde outnumbers the total events in all seven studies combined. The results of Concorde are not inconsistent with most of the results from these studies which show that zidovudine has some short-term efficacy, nor are the other trial results inconsistent with the evidence from Concorde that deferred treatment may well suffice. However, there are differences in the way that people have interpreted the findings and extrapolated from them.[25]

The results of Concorde do not encourage the early use of zidovudine as a monotherapy in symptom-free adults and have influenced the changes in the recommendations for its use in the USA.[26] Whereas previously zidovudine was recommended for all symptom-free HIV infected individuals with CD4 cell counts of between 200 and 500/µL, the current recommendations in the USA now support either continued observation (as for those with counts of above 500/µL) or initiation of zidovudine. The optimum time to start zidovudine remains unclear. Any limited benefit in disease progression has to be balanced against toxicity and the impact of the long-term use of such drugs on quality of life. Any possibility that extended use of zidovudine has an effect on mortality, in either direction, needs to be addressed in the longer term follow-up of Concorde and of the other trials and in future studies such as the proposed ComPACT trial.[27]

In view of the development of zidovudine resistance,[28] and both the limited number and efficacy of currently available drugs such as didanosine and zalcitabine, it might be advisable to defer zidovudine either until individuals develop symptomatic HIV disease or, if symptom-free, are thought to be at high risk of doing so. The medium-term to long-term benefits of the sequential use of currently available antiretroviral drugs have not yet been evaluated and combination therapy, although commonly viewed as a major advance, has not yet been shown to be more effective or safer than monotherapy. The results of current large phase III studies of combination chemotherapy, including those in Europe and Australia (Delta) and in the USA (ACTG 175 and Community Programs for Clinical Research on AIDS NUCOMBO), cannot be predicted. Finally, the whole issue of early intervention will need to be re-explored if new effective antiretroviral therapies with sustained benefit are developed.

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Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months*

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Summary

Restenosis after coronary angioplasty occurs in at least 30% of patients in the first six months and, as yet, there is no known treatment to decrease this event. We tested a monoclonal antibody Fab fragment (c7E3) directed against the platelet glycoprotein IIb/IIIa integrin, the receptor mediating the final common pathway of platelet aggregation, to see whether it reduced the frequency of clinical restenosis.

Patients who had unstable angina, recent or evolving myocardial infarction, or high-risk angiographic morphology, were randomised to receive c7E3 bolus and a 12 hour infusion of c7E3 (708 patients), c7E3 bolus and placebo infusion (695 patients), or placebo bolus and placebo infusion (696 patients). With maintenance of the double-blind state, patients were followed-up for at least 6 months to determine the need for repeat angioplasty or surgical coronary revascularisation and the occurrence of ischaemic events.

By 30 days, 12·8% of placebo bolus/placebo infusion patients had had a major ischaemic event (death, myocardial infarcton, urgent revascularisation), compared with 8·3% of c7E3 bolus/c7E3 infusion patients, yielding a 4·5% difference (35% reduction, $p = 0.008$). At 6 months, the absolute difference in patients with a major ischaemic event or elective revascularisation was 8·1% between placebo bolus/placebo infusion and c7E3 bolus/c7E3 infusion patients (35·1% vs 27·0%; 23% reduction $p = 0.001$). The favourable long-term effect was mainly due to less need for bypass surgery or repeat angioplasty in patients with an initial successful procedure, since need for repeat target vessel revascularisation was 26% less for c7E3 bolus/c7E3 infusion than for placebo treatment (16·5% vs 22·3%; $p = 0.007$). The c7E3 bolus/placebo infusion group had an intermediate outcome which was not significantly better than that of the placebo bolus/placebo infusion group.

These results extend the benefit of c7E3 bolus/c7E3 infusion from reducing abrupt closure and acute-phase adverse outcomes to a diminished need for subsequent coronary revascularisation procedures. Because this therapy carries a risk of bleeding complications and has been studied only in high-risk angioplasty patients, further evaluation is needed before it can be applied to other patient groups.

Introduction

Restenosis after balloon angioplasty and percutaneous coronary interventions is common, leading to recurrence of anginal symptoms and the need for repeat revascularisation procedures in more than 25% within 6 months, at a cost of more than $2 billion per year in the US.[1-4] The main cause of restenosis is vascular injury, induced by the inflated balloon or alternative device, accompanied by platelet-thrombus formation and change of phenotype of medial smooth muscle cells from their resting contractile state to one capable of migratory, proliferative, and secretory function.[5-7] Although various drugs have been successful in experimental models in altering the characteristic myointimal growth that occurs after vascular injury, no agent has proved effective in a large-scale clinical trial.[1,4,8,9]

Coronary angioplasty is routinely performed with adjunctive oral aspirin and intravenous heparin. However,