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CHAPTER 2

**Reductions in HIV-1 disease progression for zidovudine/lamivudine
relative to control treatments: a meta-analysis of controlled trials**

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Reductions in HIV-1 disease progression for zidovudine/lamivudine relative to control treatments: a meta-analysis of controlled trials

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Objectives
Four randomised double-blind trials have demonstrated that zidovudine/lamivudine (ZDV/3TC) reduces HIV RNA and raises CD4 counts relative to control treatments [ZDV or ZDV/zalcitabine (ddC)] .A meta-analysis of the clinical events in these trials was conducted to determine whether treatment with ZDV/3TC was also associated with a clinical benefit.

Design
The four trials, ZDV/3TC versus ZDV (NUCA3001, NUCB3001, NUCB3002) or versus ZDV/ddC (NUCA3002), were run concurrently, using the same doses of ZDV and 3TC.

Setting
Investigational sites in Europe and North America.

Patients
The trials recruited 972 HIV-1-positive, male and female patients aged $\geq$ 18 years, with CD4 counts of 100-500 cells x 10^6/l. Two trials were for ZDV-naive patients and two were for ZDV pre-treated patients.

Main outcome measures
Progression to first new Centers for Disease Control and Prevention (CDC) B or C event was compared between all ZDV/3TC arms and all control (ZDV, ZDV/ddC) arms.

Results
A total of 118 patients progressed to a first new CDC B/C event during the four trials, while 28 progressed to a new CDC C event. Meta-analysis of the trials showed a 49% reduction in progression to new CDC B/C events (relative risk, 0.509; 95% confidence interval, 0.365-0.710; $p < 0.0001$) and a 66% reduction in progression to new CDC C events (relative risk, 0.344; 95% confidence interval, 0.169-0.700; $p=0.003$) for the ZDV/3TC patients relative to the control patients. Reductions in progression to CDC B/C disease were seen in subgroups of naive and pre-treated patients, those with high and low CD4 counts and symptomatic and asymptomatic patients.

Conclusions
ZDV/3TC combination treatment delays the progression of CDC B/C disease compared with control treatments. In view of the low incidence of CDC C events, the results for progression to CDC C disease should be interpreted with caution.

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Introduction

Several antiretroviral treatments have shown a clinical benefit in terms of reduced rates of progression to AIDS or improved survival[1,2]. For other more recently developed antiretrovirals, evidence of efficacy is limited to effects on CD4 counts and HIV-1 RNA [3,4]. There is increasing evidence that CD4 counts and HIV-1 RNA are strong predictors of progression to AIDS and death[5,6], and that treatment-induced rises in CD4 count and reductions in HIV RNA correlate with reduced rates of HIV -disease progression[7,8]. Until definitive validation of these prognostic markers is forthcoming, however, demonstration that an antiretroviral reduces the rate of progression to AIDS and death will remain the definitive evidence of drug efficacy.

Four surrogate marker studies of combination zidovudine/lamivudine (ZDV/3TC) were conducted in Europe[9,10] and North America[11,12], recruiting zidovudine-naive and pre-treated patients with CD4 counts of 100-500 cells x 10^6/l. The primary objective of these trials was to evaluate the antiviral activity of the combination by measuring changes in virological and immunological markers. The individual trials were not statistically powered to detect differences in clinical-disease progression between the ZDV/3TC combination and control arms, although the evaluation of HIV -disease progression was a secondary objective for all the trials.

In all four trials, the combination of ZDV and 3TC led to a significantly greater reduction in viral load, together with greater and more sustained rises in CD4 count, compared with the control treatments of ZDV monotherapy or ZDV /zalcitabine (ddC). Additionally in three of the studies which evaluated two different dosages of 3TC in combination with ZDV there was no difference between the 150 mg twice daily and the 300 mg twice daily dosages of 3TC, with respect to CD4 responses and HIV-1 RNA.

In order to determine whether ZDV/3TC is also associated with a clinical benefit, a meta-analysis of the Centers for Disease Control and Prevention (CDC) B/C events in the four trials was conducted.

Methods

Trial designs
The aim of the meta-analysis was to combine the clinical data from all randomised Phase II trials of ZDV/3TC. Overall, 972 patients were recruited to the four Phase II trials of ZDV/3TC between March 1993 and March 1994. A summary of the designs of the four trials of ZDV/3TC is given in Tables 1 and 2. All four trials were multi-centre, placebo-controlled, double blind and randomised. The primary objective of each trial was to detect a benefit of ZDV/3TC over the control treatment in rises in CD4 count and reductions in viral load. Analysis of HIV-1 disease progression was a secondary objective for all the trials. The control treatment was ZDV in three trials (NUCA3001,NUCB3001, NUCB3002) and ZDV /ddC in one trial (NUCA3002). The NUCA3001 trial also included a 3TC-monotherapy arm.

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Table 1. Design of trials.

	Trial			
	NUCA3001	NUCA3002	NUCB3001	NUCB3002
Sample size (n)	366	254	129	223
Location	North America	North America	Europe	Europe
Trial duration – median (weeks)	68	57	48	48
Entry CD4 cells x 10^6/l	200-500	100-300	100-400	100-400
ZDV pre-treatment	< 4 weeks	> 6 months	< 4 weeks	> 6 months
Years of age [mean (range)]	35 (20-62)	37 (22-64)	35 (22-58)	38 (19-66)
Sex (% male)	87	83	74	83
Baseline CD4 count (cells x 10^6/l	350	220	270	250
Baseline disease stage				
CDC A (%)	77	58	64	53
CDC B (%)	18	30	27	38
CDC C (%)	5	12	9	9

ZDV, Zidovudine; CDC, Centers for Disease Control and Prevention.

Table 2. Baseline characteristics and progression of CDC B/C disease by treatment arm.

Trial	Treatment arm	N	Baseline CD4 count (cells x 10^6/l)	Baseline asymptomatic (%)	On trial CDC B/C events*	On trial CDC C events*
NUCA3001	ZDV	93	349	79	18 (32)	3 (3)
	3TC	87	340	76	13 (24)	4 (6)
	ZDV/3TC (150 mg)	92	366	74	4 (10)	0 (0)
	ZDV/3TC (300 mg)	94	380	80	10 (13)	1 (1)
NUCA3002	ZDV/ddC	86	229	57	19 (45)	4 (5)
	ZDV/3TC (150 mg)	84	212	57	11 (36)	0 (1)
	ZDV/3TC (300 mg)	84	203	58	14 (33)	2 (3)
NUCB3001	ZDV	64	262	66	10 (18)	2 (4)
	ZDV/3TC (300 mg)	65	280	62	5 (10)	1 (1)
NUCB3002	ZDV	73	248	47	14 (35)	8 (11)
	ZDV/3TC (150 mg)	75	253	59	6 (18)	4 (5)
	ZDV/3TC (300 mg)	75	247	53	7 (20)	3 (3)

* Total number of patients progressing to a first new event, total number of new and recurrent events in parentheses. ZDV, Zidovudine; 3TC, lamivudine; ddC, zalcitabine; CDC, Centers for Disease Control and Prevention

Two trials were conducted in patients with less than 4 weeks of prior zidovudine, and two trials in patients with at least 6 months of prior zidovudine. Prior treatment with other antiretrovirals was an exclusion criterion for all trials. For the two trials of naive patients, over 90% of the study population had no prior zidovudine experience. The screening CD4 inclusion criteria were 100-300 cells x 10^6/l for NUCA3002, 200-500 cells x 10^6/l for NUCA3001, and 100-400 cells x 10^6/l for the two European trials (NUCB3001, NUCB3002). The major inclusion and exclusion criteria were common to all the trials[9-12]. Guidelines for prophylaxis of opportunistic infections were similar across the trials.

The dosage of ZDV, either as monotherapy or in combination with 3TC or ddC, was 200 mg three times daily. The dosage of 3TC was either 150 mg or 300 mg twice daily; ddC was given at the standard dosage of 0.75 mg three times daily.

For the two North American trials, patients were randomised to 24 weeks of treatment, and then remained on their original randomised treatment until the last patient enrolled had completed 24 weeks of the trial. For the European trials, patients were randomised to an initial 24-week interval of either ZDV/3TC or ZDV, and subsequently all patients were offered open-label treatment with ZDV/3TC. The trials were completed. in late 1994 (NUCB3001, NUCB3002) and early 1995 (NUCA3001 NUCA3002).

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Classification of CDC category B/C disease

Identical case-report forms were used to collect data on CDC B/C events prospectively during the course of the trials. Data on past and current HIV-1 disease events were reviewed under blinded conditions and classified according to the CDC criteria for class B/C events, according to the 1992 CDC guidelines[13]. Repeated reports of the same CDC class B/C event were recorded as separate events only if the prior episode had resolved before onset of the subsequent event. For the purposes of the analysis, all cases of peripheral neuropathy classified by the investigator as at least possibly related to trial medication were excluded.

All CDC class C events from the four trials were reviewed by an external physician blinded to the treatment code. Further information was requested by the investigator where necessary to support the diagnosis. Endpoints were rejected from the primary analysis if there was insufficient clinical documentation to support the diagnosis.

Statistical methods

The intent-to-treat method was used, including all data from patients randomised regardless of withdrawal from randomised treatment.

Progression to new CDC B/C disease was the primary efficacy parameter, defined according to the baseline disease stage (see Table 3). A second analysis was performed including progression to new CDC class C events only.

Table 3. Progression from baseline disease stage.

Baseline disease stage	Subsequent event required for progression
Asymptomatic	CDC B, CDC class C or death
CDC B	New CDC B, CDC class C or death
CDC class C	New CDC class C or death

CDC, Centers for Disease Control and Prevention

Three meta-analyses of the HIV- 1 disease events across all four trials were conducted: (i) all four trials were pooled; (ii) North American trials were pooled; and (iii) European trials were pooled.

All analyses, were conducted using the same definition of combination and control groups: (i) combination ZDV/3TC, consisting of all high- and low-dose 3TC combination arms; and (ii) control, consisting of all other treatment arms (ZDV monotherapy, ZDV/ddC combination).

The 3TC-monotherapy arm of trial NUCA3001 was excluded from the analysis as the clinical benefit of this monotherapy has not been established. For the primary analysis, data after 24 weeks from the control arms of the European trials, after the switch from ZDV to ZDV/3TC combination treatment, was included in the control arm. The analysis was repeated excluding this data, however (see below).

Baseline disease stage was compared between groups using Fisher's exact test. The Cochran-Mantel-Haenszel test (stratified by trial) was used to determine the relative risk of progression to a first new CDC B/C event; 95% confidence intervals (CI) for this relative risk were constructed using PROC FREQ in SAS[14]. The time to first progression to new CDC class B and class C events was compared using the log-rank test (stratified by trial). The Cochran-Mantel-Haenszel Analysis of Variance (ANOVA) test statistic (stratified by trial) was used to compare the total number of new and recurrent CDC class B and class C events, regardless of baseline disease stage; for this analysis patient data on second and subsequent events were included[15]. The Breslow-Day test was used to investigate the degree of treatment effect homogeneity across trials[16]. These methods were then repeated using the endpoint of progression to CDC C events only.

Several sensitivity analyses were performed. For the analysis of progression to first new CDC B/C event, patients who withdrew from the trial were classified as progressions in order to test the effect of withdrawal on the CDC B/C endpoint. For both the CDC B/C and the CDC C endpoints, an 'As-Treated' analysis was conducted, excluding events which occurred after withdrawal from randomised treatment and all events occurring during the 24-48 week ZDV/3TC open-label phase of trials NUCB3001 and NUCB3002.

Results

The results are based on analysis of the 885 patients who were randomised to the four trials, excluding the 87 patients in the 3TC-monotherapy arm of trial NUCA3001. A summary of the four trials is given in Table 1. There were 316 patients in the control group and 569 patients in the ZDV/3TC combination group. The treatment arms of individual trials were well balanced with respect to baseline CD4 count and CDC disease stage (Table 2). Across the four trials, there was no difference in baseline disease stage between the combination and control groups: overall 63% of the patients were asymptomatic at baseline; 28% were in CDC class B; and 9% were in CDC class C. The incidence of progression to new CDC B/C events and new CDC C events is shown in Table 2.

Progression to CDC B/C disease

Overall, 118 patients progressed to a new CDC class B or C event in the four trials. A total of 24 patients progressed to CDC class C disease as their first progression event. An additional four patients developed AIDS after having progressed to a new CDC B event during treatment. The most frequently occurring new CDC B events were oral candidiasis and oral hairy leucoplakia, accounting for 68 of the patients who progressed. The other new CDC B events included multidermatomal herpes zoster, persistent diarrhoea and peripheral neuropathy. There was a total of 270 new and recurrent CDC B/C defining events during the course of the trials.

Figure 1 shows the relative risks (and 95% CI) of progression to first new CDC B/C events for each trial, for the European (NUCB3001, NUCB3002) and North American trials (NUCA3001, NUCA3002), and for all trials combined. The relative risks of progression are shown with 95% CI. The relative risk of progression to a new CDC class B/C event was approximately 50% lower for the ZDV/3TC group relative to the control group in each trial, and this reduction was significant in two of the trials. There was a significant reduction in disease progression for separate analyses of the North American trials (relative risk, 0.535; 95% CI, 0.355-0.804) and the European trials (relative risk, 0.466; 95% CI, 0.264-0.822).
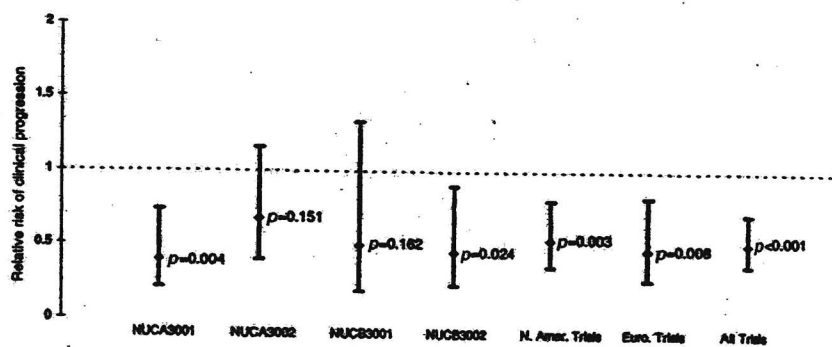

Fig. 1. Relative risk of progression to Centers for Disease Control and Prevention B/C disease in the four trials compari zidovudine/lamivudine combination with control therapy. North American trials: NUCA3001, NUCA3002; European tria NUCB3001, NUCB3002.

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The combined data from the four trials showed a 49% reduction in the progression rate for the ZDV/3TC group relative to the control group (relative risk, 0.509; 95% CI, 0.365-0.710; analysis stratified by trial). This result was also significant when the time to first progression was analysed (P < 0.0001), and for the total number of new and recurrent events occurring during the trials (P < 0.0001).

Figure 2 shows the results of subgroup analyses, dividing the patients by baseline CD4 count (under 200 versus over 200 cells x $10^6/1$), baseline disease stage (asymptomatic versus symptomatic) and prior ZDV experience (naive versus experienced). Consistent reductions of approximately 50% were shown both for patients with baseline CD4 counts- under 200 and over200 cells x $10^6/1$. Similarly the clinical benefit was apparent in patients with or without symptoms at baseline and in both ZDV -naive and ZDV -experienced patients.
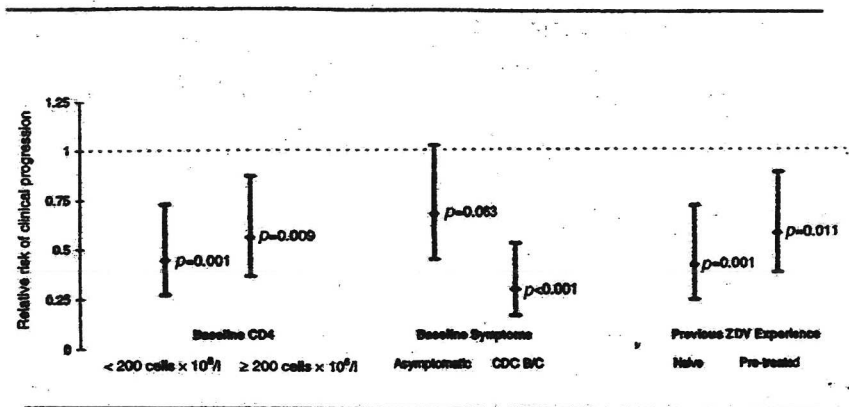

Fig. 2. Relative risk of progression to Centers for Disease Control and Prevention (CDC) B/C in subgroups. ZDV, Zidovudine.

For the sensitivity analysis, patients withdrawing from the trial were counted as progressing to CDC B/C disease. The statistical significance of the clinical benefit of ZDV/3TC was not affected by this analysis, which showed a 52% reduction in progression (p=0.002). An 'As-Treated' analysis of the data also showed significant reductions in disease progression (p=0.006).

Progression to CDC stage C disease

Twenty-eight patients progressed to a first new AIDS- defining event during the four trials: oesophageal candidiasis (10), Kaposi's sarcoma (five), *Pneumocystis carinii* pneumonia (four) , *Mycobacterium avium* complex (three), toxoplasmosis (two), progressive multifocal leukoencephalopathy (PML) (two) and recurrent bacterial pneumonia (two). There was a total of 43 new and recurrent AIDS-defining events during the course of the four trials.

Given the small number of events which occurred (Table 2), the confidence intervals are wide for the relative risk of progression to AIDS in the individual trials. Nevertheless, the relative risk of progression to AIDS was uniform and below 0.5 for all four trials considered individually. For the overall meta-analysis, the 66% reduction in progression to AIDS for the ZDV/3TC group relative to control was statistically significant (relative risk, 0.344; 95% CI, 0.169-0.700; analysis stratified by trial). This benefit was retained for analysis of the time to first progression to a new CDC C event (p= 0.003), and analysis of the total number of new and recurrent events (P= 0.002). The 'As- Treated' analysis including only those events occurring on randomised treatment, and excluding the events occurring during the 24-48 week open-label phase of NUCB3001 and NUCB3002 showed a relative risk of 0.272 (95% CI, 0.112-0.661; p= 0.004).

Results from applying the Breslow-Day test did not show evidence for heterogeneity of treatment effect between the four trials, both for analysis of progression to CDC B/C disease and for progression to CDC C disease (p > 0.10 for each comparison).

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Three out of the 972 patients died during the course of the trials. One patient died from HIV-related causes during trial NUCA3001 (PML). This patient had already been included in the analysis as having progressed to PML at an earlier time during the trial. Two patients died of non-HIV -related causes while enrolled in NUCA3001. One of these patients (treatment arm ZDV monotherapy) died from a stab wound. This death was not included in the analysis since its inclusion could have biased the results in favour of ZDV/3TC combination. The second patient (treatment arm 3TC monotherapy) died from suicide. No patients died in the other three trials.

Discussion

In each of the four trials, patients treated with ZDV/3TC showed consistent reductions in progression to new CDC B/C events relative to patients given control treatments. Meta-analysis of the four trials showed a highly significant 49% reduction in progression to new CDC B/C events, together with a 66% reduction in progression to new CDC C events for ZDV/3TC-treated patients relative to those randomised to control treatments. There were relatively few CDC C endpoints, however, and only two deaths occurred, both unrelated to HIV-1 disease progression. Given these limitations, these results cannot be seen as definitive evidence of the clinical efficacy of ZDV/3TC. A large adult clinical endpoint trial has recently been completed and has shown a 55% reduction in progression to the endpoint of CDC C disease and death for combination ZDV/3TC treatment[17]. This is very similar to the reduction shown in this meta-analysis which used the endpoint of CDC B/C disease; analysis of a European cohort study has also shown a similar 59% lower mortality associated with ZDV/3TC treatment[18].

Meta-analyses can generate useful information on treatment effects [19], particularly when designs are consistent, treatment regimens are uniform, and trial conduct methodologies are standardised. Given the large sample sizes usually involved in meta-analyses, their conclusions tend to be less prone to misinterpretation from Type I and Type II error when compared with the results of smaller individual trials. Meta-analyses, however, may have limitations if they include data from trials which differ in design and treatment regimens, or if a subset of the available or published data is used[20].

Certain aspects of these four trials make them suitable for meta-analysis. For example the four study protocols were uniform in terms of study procedures an the methods used to collect and classify CDC class B- and class C-defining events There were no other randomised Phase II trials of ZDV/3TC conducted, therefore there is no risk of selection bias in the set of four trials used for the meta-analysis. The four trials were run concurrently using the same dosages of zidovudine and 3TC and similar control arms, although the control and arm for one of the trials was ZDV /ddC, which has shown clinical benefit over ZDV monotherapy[1]. This clinical benefit would tend to bias the result of the meta-analysis against showing a clinical benefit to ZDV/3TC.

This meta-analysis included CDC B events as primary endpoints. Although these events occur earlier in the course of HIV-1 disease than CDC C events, natural history studies have shown that CDC B events are associated with an increased risk of progression to AIDS[21,22] and CDC B events have been used as primary endpoints in a large prospective trial[23]. Data from the 24-48 week phase of the European trials, when all patients received open-label treatment with ZDV/3TC, were included in the meta-analysis. These data inclusions would be expected to bias the results against the ZDV/3TC arm; the results for both the CDC B/C and CDC C endpoints remained statistically significant in a secondary analysis which excluded this data. The number of CDC C endpoints is small, but the significance attained for the analysis of progression to CDC C events alone supports the overall conclusions from analysis of the combined CDC B/C events.

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There is considerable debate as to the type of data required to prove the clinical efficacy of antiretroviral treatments. A recent meta-analysis has provided preliminary evidence that trials showing greater. CD4 benefit to treatments have also shown greater clinical benefits (Michael Hughes, personal communication, 1996), but there are cases where rises in CD4 counts have not led to a clinical benefit.[24]. For new combination treatments With substantial effects on CD4 counts and HIV-1 RNA[3], it may be difficult to maintain good compliance in long-term clinical endpoint trials against a control known to have inferior effects on CD4 and HIV RNA. Given these difficulties, meta-analysis of Phase II trials with consistent trial designs may provide an alternative method to demonstrate clinical benefit for new antiretroviral treatments. This technique has been proposed for evaluation of treatments for cardiovascular disease[25].

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