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Survival Effects of ZDV, ddI, and ddC in Patients with CD4 ≤50 cells/mm^3

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Summary: Seven major clinical trials for the treatment of HIV-infected individuals are investigated. The treatments used in these trials were zidovudine, dideoxyinosine, dideoxycytosine, and one combination for patients with CD4 cell counts <500 cells/mm^3. Patients in each trial are partitioned into two subgroups based on their baseline CD4 cell counts: patients with CD4 ≤50 cells/mm^3 and patients with CD4 >50 cells/mm^3. The difference between treatment effects, using survival as a measure of effect, within each subgroup is calculated separately for each trial; this difference is referred to as "subgroup response." For each trial the difference between the subgroup responses is calculated and standardized. A meta-analysis is conducted over all seven trials for the differences between subgroup responses; the consistency of responses is evaluated across all trials among patients within baseline CD4 subgroups. Based on the result of this meta-analysis we conclude that there is no evidence that the treatment effects in patients with CD4 ≤50 cells/mm^3 are different from those among patients with CD4 >50 cells/mm^3. This result is observed in patients with different antiviral experience and different baseline characteristics. Risk ratios as well as χ^2 statistics are used to quantify the response rates in different subgroups. Kaplan–Meier curves of survival for these trials are depicted for all patients and each subgroup separately. In most of the trials the Kaplan–Meier curves for the patients with CD4 ≤50 cells/mm^3 resemble those for all patients. This finding implies that most of the clinical events, and therefore statistical power, in the analyses of these trials came from patients with CD4 ≤50 cells/mm^3. Therefore, the exclusion of patients with CD4 ≤50 cells/mm^3 may result in prolonged and/or larger clinical trials. **Key Words:** Subgroup analysis—CD4 cell count—Hypothesis testing—Meta-analysis.

A belief held by many clinical researchers is that HIV-infected patients with advanced disease benefit minimally, if at all, from therapies currently available for the treatment of HIV. The biological arguments supporting this belief include that such patients are extremely immunocompromised and cannot respond to treatment and that because such patients typically have received prolonged courses of treatment for HIV they have developed cross-resistance to nucleoside analogue treatments (1–5).

Because researchers believe that nucleoside analogue–experienced patients with advanced disease do not benefit from treatment with nucleoside analogues (1), many clinical trials initiated in the past several years, and currently under proposal, to assess new treatments have excluded subjects with CD4 cell counts of <50 cells/mm^3 (e.g., unpublished protocols and ongoing clinical trials). The premise is that because relatively little treatment benefit is conferred upon such subjects, data from these subjects will contribute little to the overall outcome of an investigational study. Therefore the added costs,

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in both money and time, of enrolling subjects with advanced HIV infection cannot be justified. Additionally, some completed clinical trials that did not demonstrate an overall treatment effect have resulted in extensive *post hoc* analyses that excluded subjects below a certain CD4 cell count threshold (6).

To our knowledge, however, a systematic approach to assessing whether subjects with advanced HIV infection do or do not benefit from treatment with nucleoside analogues has not been performed. That is the purpose of the research presented herein. Specifically, using data available from clinical trials of nucleoside analogues, we wanted to explore whether subjects with CD4 cell counts ≤ 50 cells/mm^3 experience a treatment benefit from the investigational drug relative to the standard therapy (active control) in each trial. As we will discuss, this objective was modified to assessing whether the treatment effect among subjects with CD4 counts ≤ 50 cells/mm^3 is similar to the treatment effect among subjects with CD4 counts >50 cells/mm^3.

DESCRIPTION OF CLINICAL TRIALS

We discuss three nucleoside analogues—zidovudine (ZDV), dideoxyinosine (ddI), and dideoxycytosine (ddC). These nucleoside analogues were the only drugs approved for the treatment of HIV infection at the time of this research. The trials discussed herein were essential in The Food and Drug Administration's (FDA) approval of ZDV, ddI, and ddC (Table 1). The fourth approved nucleoside analogue, d4t, has been granted FDA accelerated approval; however, the final clinical results of this trial are not yet available.

These randomized clinical trials differ with respect to the baseline demographics and characteristics of the patients enrolled. The primary end points, population of patients, duration of therapy, and inclusion/exclusion criteria may differ among the trials. The earliest of these trials started in 1986 (BW02) (7) and the latest in 1990 (CPCRA002) (8). Because these trials were designed and conducted in different time periods, the standard of care may differ for each trial. As an example, the BW02 trial was conducted at a time when no prophylaxis for *Pneumocystis carinii* pneumonia was available. The survival analyses and the meta-analysis conducted in this research appreciate these concerns.

Data available for the analyses in this research include baseline CD4 cell counts and the survival time and survival status reported at the end of the studies. Patients in all the studies were HIV positive, and a large number of them had advanced disease, most having entry CD4 levels <150 cells/mm^3. Except study XXX, all other trials are either published in the literature or have been presented in public hearings (6–12). A brief description of these trials follows; for more information the reader is encouraged to read the published text of each study.

TABLE 1. *Description of clinical trials*

Study	Treatments	Primary end points	Previous ZDV
BW02	ZDV Placebo	Survival	No
ACTG 002	Low-dose ZDV High-dose ZDV	Survival	No
ACTG 116b/117	Low-dose ddI High-dose ddI ZDV	Progression	Yes
ACTG 114[a]	ddC ZDV	Survival	Yes
ACTG 119	ddC ZDV	Survival	Yes
XXX[b]	A B C	Progression	Yes
CPCRA 002	ddI ddC	Progression	Yes

[a] N3300 is the Roche number for this trial.
[b] Because the results of this trial are not published yet, we did not identify it by its real name.

BW02 was a phase II placebo-controlled, double-blind trial of ZDV. The study resulted in FDA approval of ZDV as the first nucleoside analogue for the treatment of HIV infection. This study was started in 1986, and the placebo arm of the study was terminated after 6 months because of a survival advantage among ZDV-treated patients (7): 19 deaths among the placebo-treated patients, one among the ZDV-treated patients. In this article we use the events up to 10 days after the termination of the placebo arm of the study.

ACTG 002 was initiated in early 1987 as a randomized double-blind study in patients with no previous ZDV experience. The study resulted in recommending a lower dose of ZDV; the recommended dose was reduced from 1,200 mg/day (used in BW02) to 600 mg/day (9). Moreover, ZDV toxicities were greater among the high-dose–treated patients. ACTG 116b/117 was a randomized, double-blind study for patients who had received a minimum of 4 months of previous treatment with ZDV (10). The study resulted in FDA approval of a lower

recommended dose of ddI, 500 mg/day, for treatment of HIV infection. This study had three treatment groups: low-dose (500 mg/day) ddI, high-dose (750 mg/day) ddI, and ZDV. ACTG 114 was a phase III randomized, double-blind clinical trial, which started in September 1989. Patients enrolled in this trial had <12 weeks of previous ZDV exposure. The study was terminated after a statistically significant difference in survival was established, with more deaths among ddC-treated patients.

ACTG 119 was a randomized, open-label study for patients who had >12 months of previous ZDV exposure. The trial failed to recruit a sufficient number of patients (i.e., the planned sample size was 315, but only 115 were recruited). This trial was terminated after 12 months. The trial XXX was a randomized, double-blind study for patients who had been exposed to ZDV for >6 months. The results of this study are not published yet, so we do not use its ACTG number. CPCRA 002 was an open-label study for patients who could not tolerate ZDV or failed treatment with ZDV. This study started in 1990, and it resulted in FDA approval of monotherapy ddC for patients who could not tolerate ZDV or who failed treatment with ZDV. In the next section we present the methodology to analyze these trials individually and via a meta-analysis approach.

METHODS AND RESULTS

Survival is the clinical end point used herein. The intent-to-treat approach is used, i.e., all those patients who were randomized and for whom baseline CD4 and the final status were available are included in the analyses. Two studies, ACTG 116b/117 and XXX, had three treatment groups, two of which are now approved. For these two studies we included the approved doses or treatments in the survival analyses; in the Kaplan–Meier curves we depict all three arms of these studies. As an example, in study ACTG 116b/117 we consider only ZDV and low-dose (500 mg) ddI in our analyses, because ZDV is approved and the only approved dose for ddI is the low dose. But the Kaplan–Meier curves for all three groups (ZDV, high-dose ddI, and low-dose ddI) are depicted.

In this investigation we evaluated 3,882 HIV-infected individuals from seven major randomized clinical trials. Fourteen hundred fourteen patients who participated in these trials had baseline CD4 counts ≤ 50 cells/mm^3. There were 1,071 deaths in these trials; 615 of them were patients with baseline CD4 ≤ 50 cells/mm^3. The number of deaths was lower in patients with baseline CD4 >50 cells/mm^3 of 2,468 patients in this subgroup 455 died. In general, for the same period of time more patients with baseline CD4 ≤ 50 cells/mm^3 died than patients with CD4 >50 cells/mm^3 regardless of treatment and other baseline characteristics.

For each study patients are partitioned into two subgroups: patients with baseline CD4 ≤ 50 cells/mm^3 and patients with baseline CD4 >50 cells/mm^3. Table 2 lists the total number of patients in each subgroup along with the total number of deaths. For descriptive purposes, Kaplan–Meier curves are used to depict the survival rates; estimates of risk ratios and 95% confidence intervals are presented for each trial. To have sufficient power in conducting statistical analyses using all the data, meta-analysis is used. These three approaches and their results are discussed in the following text.

Kaplan–Meier Curves

The Kaplan–Meier curves presented herein depict the survival rates of the seven trials for all patients and for each CD4 subgroup. Formal hypothesis testing was not conducted because survival was not the primary end point in all of these trials. Figures 1–7 depict the Kaplan–Meier curves for the seven trials described in Table 1. Each graph is numbered and augmented with a letter *a*, *b*, or *c*. The numbers are the same numbers used for each trial in Table 1. The graphs with letter *a* depict the Kaplan–Meier curves for all patients, and the graphs with letters *b* and *c* depict the curves for patients with CD4 ≤ 50 cells/mm^3 and CD4 >50 cells/mm^3, respectively.

The main purpose of these graphs is to present a graphic comparison of the survival curves be-

TABLE 2. *Total number of deaths/number of patients in each trial*

Study	All patients	CD4 ≤ 50 cells/mm^3	CD4 >50 cells/mm^3
BW02[a]	27/250	15/105	12/145
ACTG 002	411/501	180/218	231/283
ACTG 116B/117	128/913	80/293	48/620
ACTG 114	92/635	50/191	42/444
ACTG 119	53/115	32/45	21/70
XXX	172/1.001	108/283	64/718
CPCRA 002	187/467	150/279	37/188

[a] The events up to 10 days after the termination of the study are included. The survival status of 29 patients was recorded in the database; they are not included in the analyses.

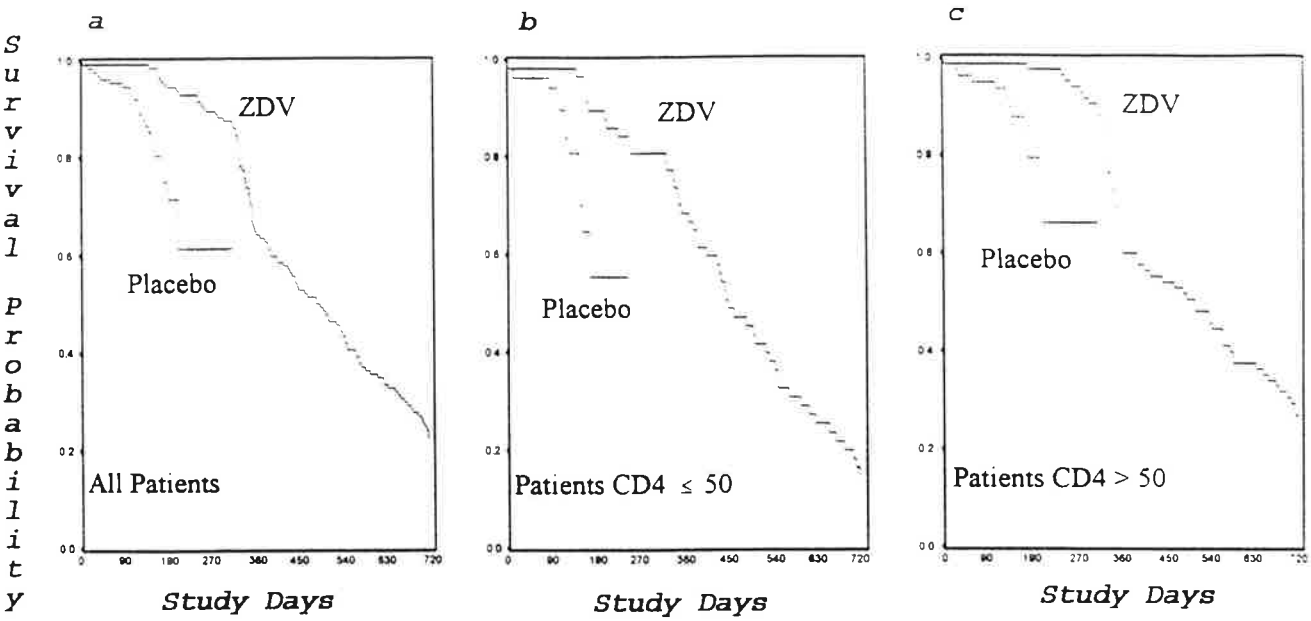

FIG. 1. BW02 trial, Kaplan–Meier (K–M) curves for a placebo-controlled randomized trial. The placebo arm stopped after 6 months. **(a)** K–M represents all patients; **(b, c)** CD4 subgroups. The observed patterns of survival rates are similar in all three.

tween treatment groups for each trial and within each subgroup. For a given trial the scales of the x-axes are similar and represent the days that patients were under study. The y-axes depict the proportion of patients who were alive at the end of the trial. For a given trial these curves can be compared visually by observing the trend of the curves and the position of the curve of one treatment compared with the other treatment for all patients and for each subgroup or even across subgroups.

These graphs also present the observed differ-

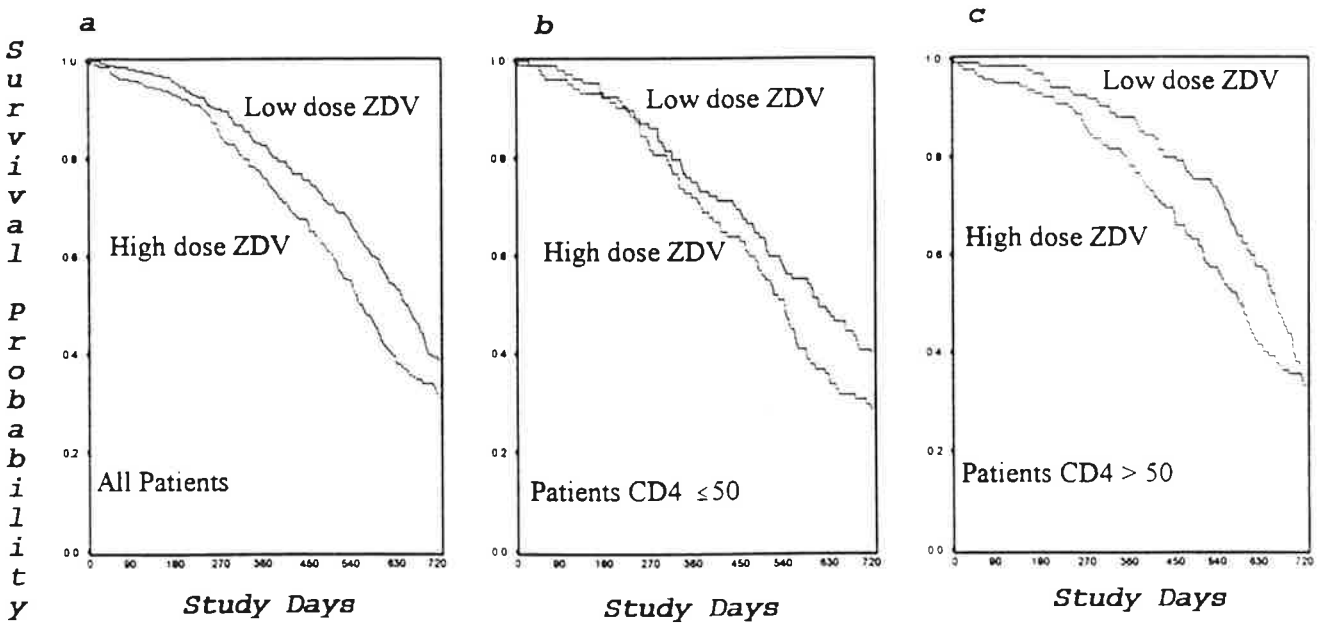

FIG. 2. ACTG 002 trial, Kaplan–Meier (K–M) curves to compare low doses and high doses of ZDV in patients with no previous ZDV experience. **(a)** K–M represents all patients; **(b, c)** CD4 subgroups. In all three graphs the observed risks for patients at low dose are less than the observed risks for patients at high dose. This difference is not statistically significant.

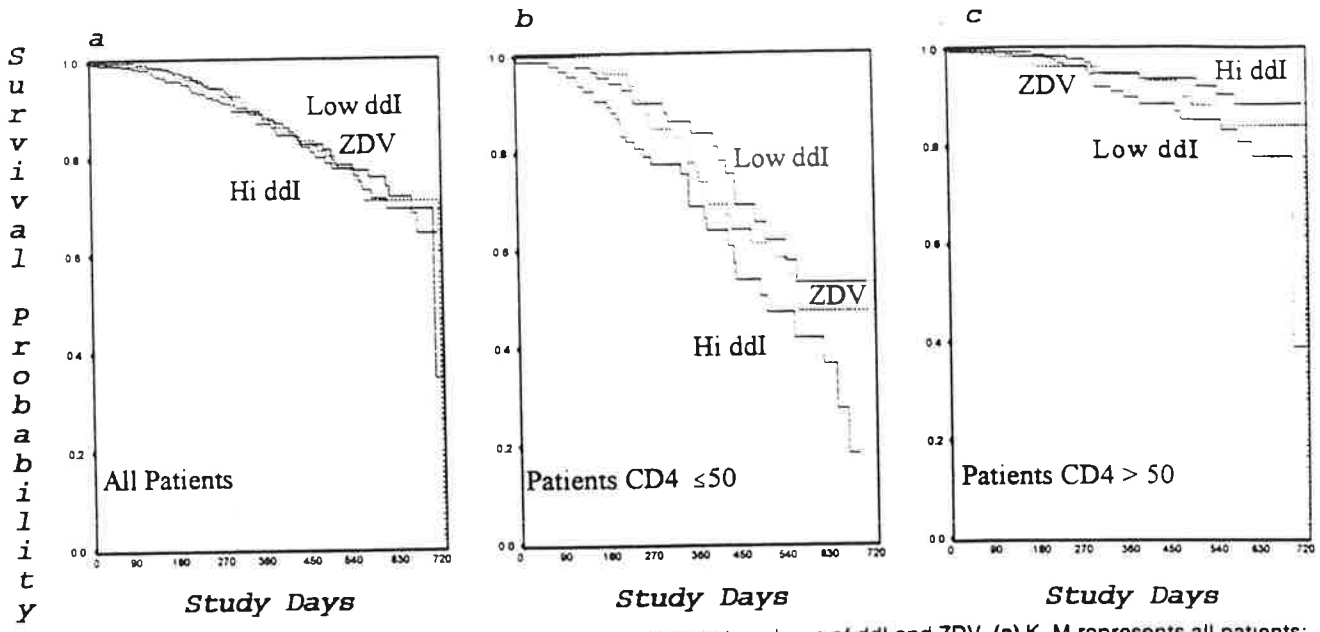

FIG. 3. ACTG 116b/117 trial, Kaplan–Meier (K–M) curves to compare two doses of ddI and ZDV. **(a)** K–M represents all patients; **(b, c)** CD4 subgroups. This is the only trial in which interaction between the treatments and the CD4 subgroups was observed.

ences in the survival rates between the two subgroups within each trial. Patients with baseline CD4 ≤ 50 cells/mm^3 have higher rates of death compared with patients with baseline CD4 >50 cells/mm^3 regardless of the trial and the treatment group. This finding shows that baseline CD4 is an excellent prognostic factor, which is in agreement with the published literature in this area (e.g., 1,8). From the Kaplan–Meier curves it can be observed that with respect to survival, the treatment differences for patients with CD4 ≤ 50 are similar to the treatment differences for all patients. These treatment differences in survival are quantified in a risk ratio analysis described herein.

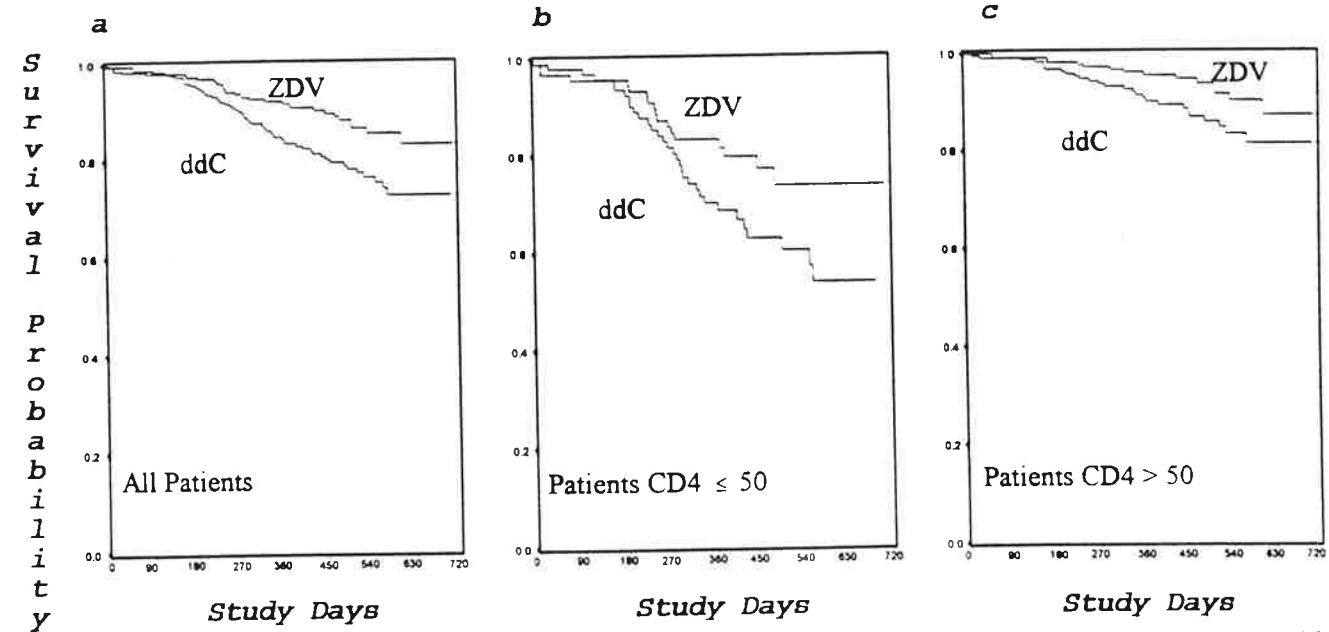

FIG. 4. ACTG 114 trial, Kaplan–Meier (K–M) curves to compare ZDV and ddC in patients with <4 months of ZDV experience. **(a)** K–M represents all patients; **(b, c)** CD4 subgroups. The observed relative survival rates between treatments are fairly similar in each CD4 subgroup.

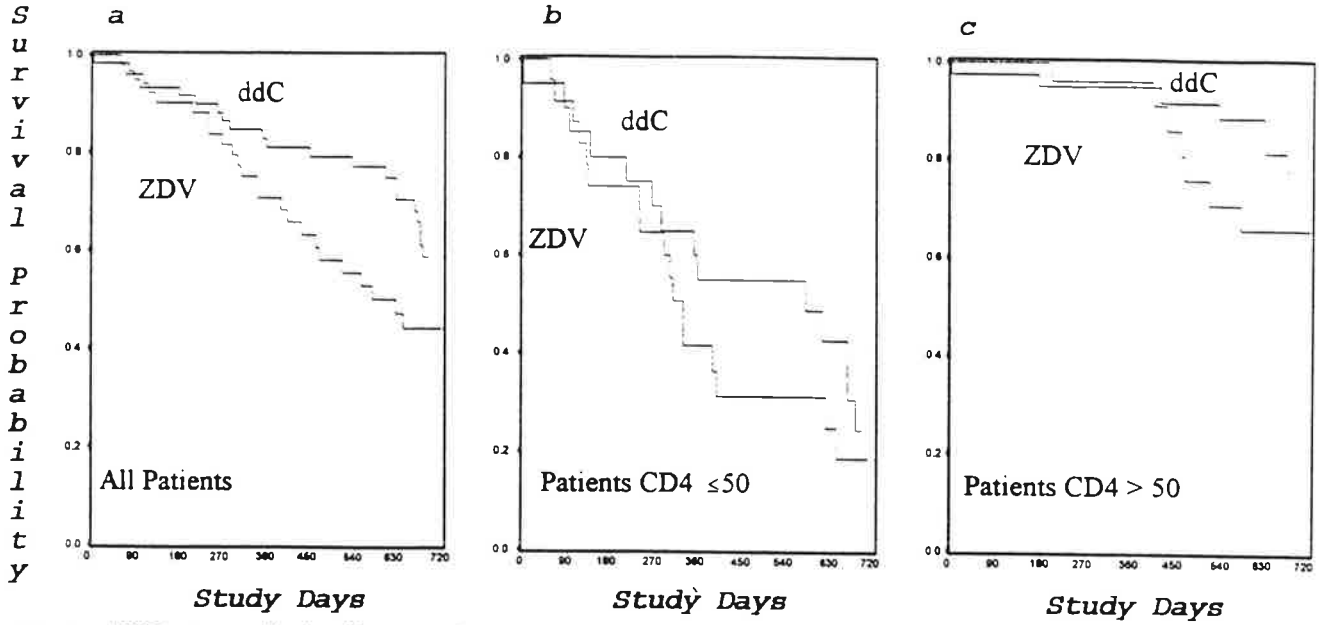

FIG. 5. ACTG 119 trial, Kaplan–Meier (K–M) curves to compare ZDV and ddC in patients with >12 months of ZDV experience. **(a)** K–M represents all patients; **(b, c)** other CD4 subgroups. The observed relative survival rates between treatments are fairly similar in each CD4 subgroup. This trial stopped before accruing the planned sample size.

Risk Ratio Analyses

Three survival analyses are presented for each trial: all patients, patients with CD ≤50 cells/mm^3, and patients with CD4 >50 cell/mm^3. The survival analyses are conducted with treatment as the only factor in the model; no covariate is used. For each analysis we estimate a risk ratio and its 95% confidence interval. Some of these analyses have been published and are available in the literature or have been presented in public meetings (6–12). We have redone the analyses because some trials did not use

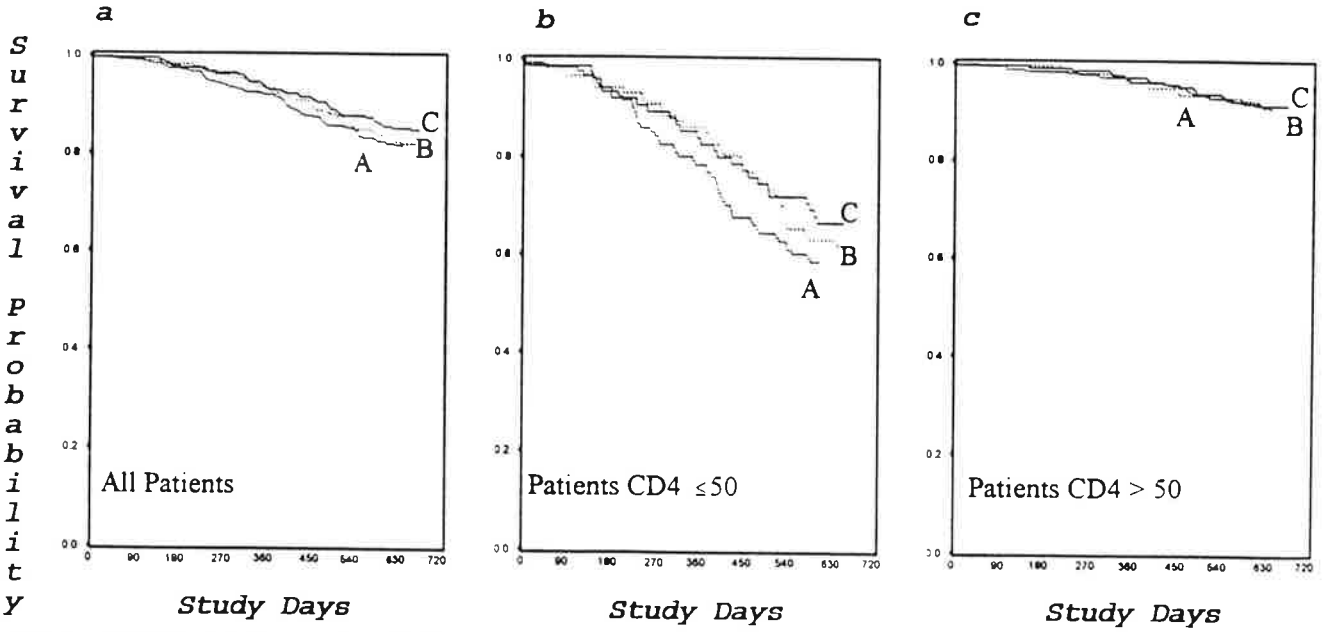

FIG. 6. The XXX trial, Kaplan–Meier (K–M) curves to compare treatments A, B, and C. **(a)** K–M represents all patients; **(b, c)** CD4 subgroups. The observed relative survival rates between treatments are fairly similar in each CD4 subgroup.

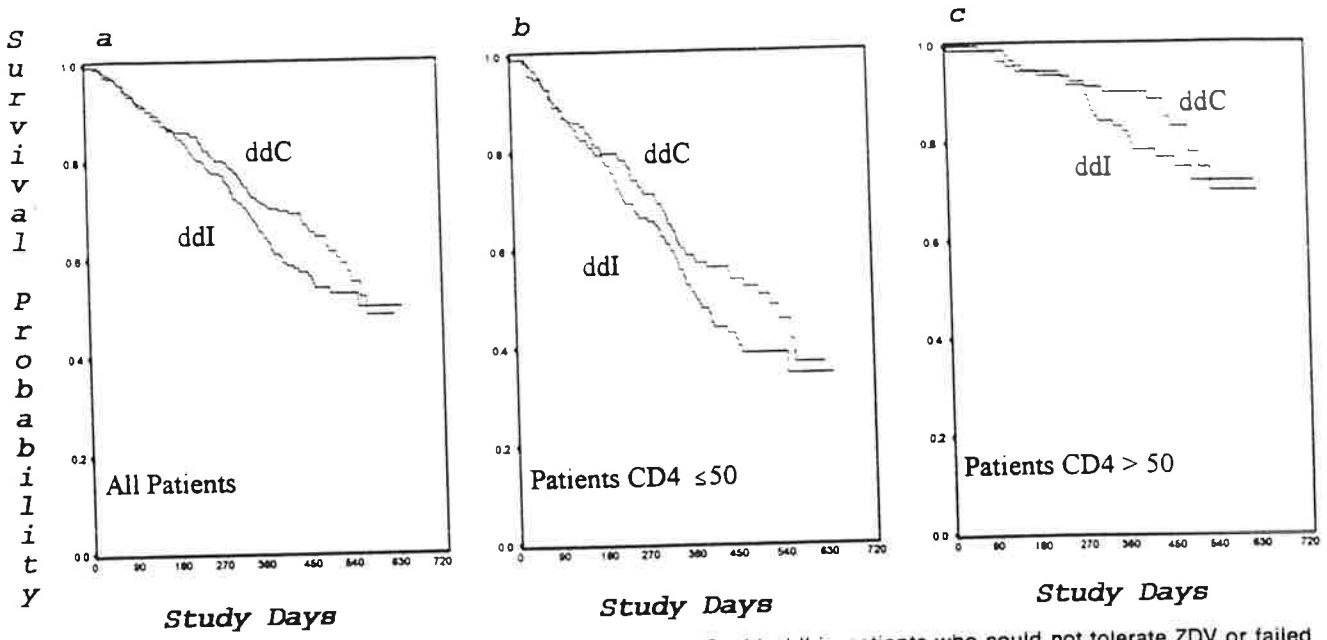

FIG. 7. CPCR002 trial, Kaplan–Meier (K–M) curves to compare ddC with ddI in patients who could not tolerate ZDV or failed treatment with ZDV. (a) The K–M represents all patients; (b, c) CD4 subgroups. The observed relative survival rates between treatments are fairly similar in each CD4 subgroup. Patients in this trial were in late stages of the disease, so the number of events is larger in this trial compared with other trials.

survival as the primary end point or the data were analyzed with one or several covariates in the models (8,9).

Table 3 lists the risk ratio analyses for all patients and the CD4 subgroups in all seven trials. The main purpose of this table is to compare the risk ratios of two treatment groups in each trial when all patients are in the model and when only a subgroup of patients are in the model. Note that some of these trials were designed for a primary end point other than survival, and none of them was designed for subgroup analyses. The last column of this table should be viewed with this caveat in mind.

The first column of Table 3 lists the trials and the *treatments* used in the trials. The order in which these treatments appear in this list is very important in the reading of Table 3. The risk of death among patients who have taken the second treatment in the list constitutes the numerator of the risk ratios. A risk ratio of 1 means the observed risks in both treatment groups are the same. A risk ratio >1 implies that the observed risk of death among patients who took the second treatment in the list is larger than the risk among patients who took the first treatment; the converse is true when the risk ratio is <1. Risk ratios should not be compared across trials; rather they should be compared only within each trial. This is because the population of patients and other baseline characteristics differ from one trial to the next and because different trials may have different treatments. For each trial the risk ratios and the 95% confidence intervals for all patients and for each subgroup are presented in the last column of Table 3. These analyses exclude patients for whom baseline CD4 and/or the final status were not known.

For each trial, except ACTG 116b/117, all three observed risk ratios are either >1 or <1. This observation suggests that the treatment effect for patients with baseline CD4 ≤50 cells/mm^3 is consistent with that for patients with baseline >50 cells/mm^3. ACTG 116b/117 is the only trial for which this pattern does not hold. In this trial the risk ratios are 1.09, 1.68, and 0.50 for all patients, patients with baseline CD4 ≤50 cells/mm^3, and patients with baseline CD4 >50 cells/mm^3, respectively. The risk ratio changes from 1.68 to 0.5 when we go from one subgroup to the next. A similar pattern is observed in the K-M curves of this trial (Fig. 3). This reversal may be interpreted to mean that patients with CD4 ≤50 cells/mm^3 are at higher risk of mortality if they take the high-dose ddI but those with CD4 >50 cells/mm^3 are at lesser risk if they take this dose; this reversal may also be just the result of conducting subgroup analysis. We should reiterate that this study was not designed for subgroup analyses, and

TABLE 3. *Survival risk ratios of all patients and subgroups*

Study[a]	Patients	Risk ratio	95% CI
BW 02 (ZDV vs. Placebo)	All	6.76	(4.93, 9.23)
	≤50	9.32	(5.47, 15.88)
	>50	5.71	(3.86, 8.45)
ACTG 002 (Low ZDV vs. high ZDV)	All	1.21	(1.00, 1.47)
	≤50	1.26	(0.94, 1.69)
	>50	1.15	(0.89, 1.49)
ACTG 116B/117 (ZDV vs. Low ddI)	All	1.09	(0.71, 1.66)
	≤50	1.68	(0.96, 2.95)
	>50	0.50	(0.25, 1.03)
ACTG 114 (ZDV vs. ddC)	All	1.76	(1.15, 2.71)
	≤50	1.54	(0.86, 2.77)
	>50	2.00	(1.06, 3.76)
ACTG 119 (ddC vs. ZDV)	All	1.71	(1.01, 2.88)
	≤50	2.14	(0.62, 7.43)
	>50	1.82	(1.00, 3.32)
XXX (A vs. B)	All	0.85	(0.57, 1.28)
	≤50	0.82	(0.48, 1.38)
	>50	0.89	(0.46, 1.72)
CPCRA 002 (ddI vs. ddC)	All	0.76	(0.57, 1.01)
	≤50	0.76	(0.55, 1.05)
	>50	0.72	(0.39, 1.35)

[a] The order in which these treatments appear in this list should be considered when reading this table. These are the results of Cox proportional analyses. The risk of death among patients who have taken the second treatment in the list constitutes the numerator of the risk ratios. A risk ratio of 1 means the observed risks in both treatment groups are the same. A risk ratio >1 implies that the observed risk of death among patients who took the second treatment in the list is larger than the risk among patients who took the first treatment; the converse is true when the risk ratio is <1.

a second study should confirm these results. We discuss the potential for interaction between treatment and baseline CD4 cell counts in the discussion section.

We caution the reader about the usage and the interpretation of the last column of Table 3. This column should be used as inferential statistics only if the trial is designed with sufficient power and with survival as its primary clinical end point; otherwise the confidence intervals should be used as exploratory statistics for supportive evidence and to generate hypotheses. These findings should not be used as confirmed results; independent trials should be conducted to confirm these findings. This is especially true for the subgroups; none of these trials was designed to conduct subgroup analyses.

TABLE 4. *CD4 ≤50 cells/mm³*

Status	Standard treatment	New treatment
Dead	n1	n2
Alive	N1-n1	N2-n2
Total	N1	N2

Meta-Analysis

A suitable method to answer the main question of this research is meta-analysis. The main question was "Is there a *treatment effect* in patients with CD4 ≤ 50 cells/mm³?" *Treatment effect* here refers to the difference between the standard and the investigational dose or treatment within each trial. In meta-analysis, data from several clinical trials are used to gain more statistical power to detect a moderate treatment effect and to obtain a better estimate for the treatment effect (13–15). This method assumes that there are enough clinical trials available to "combine" the data and conduct a meta-analysis to answer the question on the efficacy of the nucleoside analogues in patients with CD4 ≤50 cells/mm³. But the paucity of AIDS clinical trials investigating the same treatments and insufficient numbers of patients in each subgroup to allow comparisons of two treatments forced us to modify the main question. The modified question became "Within each trial, is there any difference in treatment effects between patients with baseline CD4 >50 cells/mm³ and those with CD4 ≤50 cells/mm³?"

To address this question we constructed for each trial two 2 × 2 tables (Tables 4 and 5), one per subgroup of patients. The meta-analysis approach we used is based on calculating the difference in number of deaths between the standard and the new treatment in each subgroup and within each trial. Within a subgroup the difference between treatments with respect to survival is called a "subgroup response." In each 2 × 2 table the number of deaths between the two treatment groups are compared using χ^2 statistics. An additional χ^2 statistic is constructed to compare the difference between the two subgroup responses within each trial.

The following two variables are introduced to quantify the difference between the observed and the expected number of deaths (i.e., indirectly this is a measure of difference between the standard and the new treatment):

$$Z1 = O1 - E1 \text{ and } Z2 = O2 - E2$$

TABLE 5. *CD4 >50 cells/mm³*

Status	Standard treatment	New treatment
Dead	m1	m2
Alive	M1-m1	M2-m2
Total	M1	M2

where O1(=n1) and O2(=m1) are the observed number of deaths for standard treatment in subgroups 1 and 2, respectively, and E1 and E2 are the expected number of deaths for standard treatment in each subgroup, assuming the null hypothesis is correct (i.e., the standard and the new treatment have similar effects). The total number of patients with baseline CD4 ≤50 is N1 + N2, N1 being in the standard treatment group and N2 in the new treatment group; the total number of patients with baseline CD4 >50 is M1 + M2, M1 being in the standard treatment group and M2 in the new treatment group.

The null hypothesis is that the treatments have the same survival response, and the alternative is that they have a different survival response. Under the null hypothesis Z1 and Z2 each will differ only randomly from zero; these values can be standardized and compared with tabulated values. If the value of Z1 is close to zero, the difference between the two treatments in subgroup 1 is not significant, and if it is far from zero, one may claim that there is a significant difference between two treatments in this subgroup. The same is true for Z2, which is the difference between two treatments in subgroup 2. One may use the Type I error rate of 0.05 to decide whether Z1 and Z2 are close to zero or far from zero.

Although we report the χ^2 results for each subgroup, we are interested in the values of D = Z1 − Z2, the difference between the treatment responses in the subgroups. The absolute value of this quantity, D, will be large if and only if the values of Z1 and Z2 are not close both in their signs and their magnitudes. In a given trial if the signs of Z1 and Z2 change from one CD4 subgroup to the next, it means that the treatments may have different effects in different subgroups. If the treatment response is very small in one subgroup and very large in the other, it signals the fact that the treatments may have effects in one subgroup but not in the other subgroup. Or, in a worst-case scenario, the drug may be efficacious in one subgroup and harmful in the other subgroup.

The magnitude and the signs of Z1, Z2, and D are only meaningful within each trial. Because the treatments in one trial may differ from the other trials, and the population of patients and other baseline characteristics differ among trials, one should not compare these values across the trials. To make these quantities comparable across trials we standardized them (i.e., squared and divided by their variances). These standardized quantities have the property of being approximately χ^2 with one degree of freedom for each trial and each subgroup (16). Furthermore, because these trials are independent, the sum of these χ^2 will generate χ^2, with seven degrees of freedom.

The results of these χ^2 values for each trial and each group are presented in Table 6; the pooled χ^2 values are also presented in this table for each subgroup and the differences. Based on the results of the meta-analysis presented in Table 6, there is no evidence of any difference between the two CD4 subgroups with respect to the treatment effects on survival. The pooled χ^2 is 3.5, which is not statistically significant ($p > 0.25$). Furthermore, the pooled χ^2 for the subgroup with CD4 ≤ 50 cells/mm^3 is statistically significant ($p < 0.025$).

DISCUSSION AND CONCLUSION

Across the seven clinical trials investigated, the Kaplan—Meier curves showed that the survival rates among patients with baseline CD4 >50 cells/mm^3 were consistently greater than the rates among patients with baseline CD4 ≤50 cells/mm^3 regardless of the treatments and populations studied in the clinical trials. Three separate but related questions with respect to the treatment effects may be asked. Is there a treatment effect in patients with CD4 ≤50 cells/mm^3? Is there a treatment effect in patients with CD4 >50 cells/mm^3? Does the treatment effect differ between the two subgroups? We used χ^2 and pooled χ^2 statistics (16,17) to answer these questions for each trial (Table 6). Note that because these trials were not designed to conduct a statisti-

TABLE 6. χ^2 *Values for each CD4 subgroups and the treatment CD4 interaction*

Study	χ^2 values: CD4 >50 cells/mm^3	χ^2 values: CD4 ≤50 cells/mm^3	Interaction[a]
BW02 (ZDV vs. placebo)	7.86	6.04	0.01
ACTG002 (Low ZDV vs. high ZDV)	0.25	0.78	0.04
ACTG116B/117 (ZDV vs. low ddI)	0.55	1.87	2.25
ACTG114 (ZDV vs. ddC)	3.78	4.33	0.01
ACTG119 (ZDV vs. ddC)	0.27	0.02	0.11
XXX (A vs. B)	0.03	0.37	0.11
CPCRA002 (ddI vs. ddC)	0.59	2.79	0.98
Pooled χ^2 (df = 7)	13.33	16.20	3.50

[a] This column displays the calculated χ^2 valves of the interaction between treatments and subgroups.

cal test within each subgroup, the χ^2 tests may not have sufficient power to answer each question. Therefore, in our research, we emphasized the pooled χ^2 test with seven degrees of freedom.

The results of this meta-analysis show that we do not have any evidence that the treatment response (i.e., difference between the standard and the new treatment) in patients with CD4 $\leq$50 cells/mm^3 is different from that of patients with CD4 >50 cells/mm^3. For each of the seven trials, the χ^2 statistic that tests the interaction between the treatments and the CD4 subgroups, the last column in Table 6, was not statistically significant for any one trial. ACTG 116b/117 is the only trial for which this χ^2 is >1, but still it is not significant considering the commonly used significance level of 0.05. The same finding was confirmed when we conducted a meta-analysis by pooling these seven independent χ^2 statistics. Although we did not use a meta-analysis for the risk ratios analysis, in general these analyses confirm the above-cited findings. Based on these seven randomized clinical trials, most of the events (i.e., deaths) occurred in patients with CD4 $\leq$50 cells/mm^3. Furthermore, the number of events is the driving force in statistical power and sample size calculation in designing these clinical trials. In designing a clinical trial to detect a specified level of difference in survival rates between two treatment groups, a trial may need to be continued longer and/or the sample size may need to be increased if patients with CD4 $\leq$50 cells/mm^3 are excluded.

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